IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re: United States Patent

No. 4,826,868

: Attn: Box Patent Ext.

Inventors: Michael P. Wachter, and

Michael P. Ferro

Issue Date: May 2, 1989

RECEIVED

MAY 2 9 2003

OFFICE OF PETITIONS

Commissioner of Patents PO Box 1450 Alexandria, VA 22313-1450

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,826,868 and duplicate copies of the papers thereof (for a total of three copies), certified as such.

Also submitted herewith is an original declaration for extension of U.S. Patent No. 4,826,868 and an Associate Power of Attorney. Therefore, the present application is complete and entitled to a filing date of May 29, 2003.

06/05/2003 CKHLOK 00000024 100750 4826868

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Pursuant to the provisions of 37 C.F.R. §1.740(b)(2), the undersigned appointed attorney for applicant, Ortho-McNeil Pharmaceutical, Inc. (Ortho) states that Ortho is the owner of U.S.Patent No. 4,826,868, by virtue of the assignment (see page 1 of Request) (see Exhibit I); that Schering-Plough Animal Health ("SPAH"), a wholly-owned subsidiary of Schering Corporation, is the holder of the regulatory approval granted with respect to Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets as evidenced by: 1) submission on October 25,1996 by SPAH of INAD No. 9916 to the Center for Veterinary Medicine ("CVM") of the Food and Drug Administration for the purpose of conducting clinical studies for the use of tepoxalin for treating inflammatory conditions in dogs (see Exhibit VI); (2) the submission on December 20, 2001 by SPAH of NADA No. 141-193 for tepoxalin(see Exhibit VIII); and the CVM letter dated March 31, 2003 approving NADA No. 141-193 for Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets for the control of pain and inflammation associated with osteoarthritis in dogs(see Exhibit II).

The Commissioner is hereby authorized to charge payment in the amount of \$1,120.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 10-0750/ORT-518/ECC. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

EYlen Ciambrone Coletti Registration No. 34,140

Attorney for Assignee of Record Telephone No. (732)524-2359

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
Patent Department
New Brunswick, New Jersey 08933-2359

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Michael P. Wachter and Michael P. Ferro	
U.S. Patent No. 4,826,868	RECEIVED
	MAY 2 9 2003
Issue Date: May 2, 1989	OFFICE OF PETITIONS
Date of Deposit: May 29, 2003	
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I hereby certify that the original Request for Patent Term	
X, Associate Power of Attorney, Declaration and Transm	
certified copies (2) of same are being submitted to Karin	
indicated above and are addressed to the Commissioner of	of Patents, PO Box 1450,
Alexandria, VA 22313.	
	•
•	
Victoria Schellin	20)
(Typed or printed name of person depositing papers or for	
Oristain Scholli	
(Signature of person depositing papers or fee)	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re: United States Patent

No. 4,826,868

: Attn: Box Patent Ext.

Inventors: Michael P. Wachter, and

Michael P. Ferro

.

Issue Date: May 2, 1989

: Y-----X

Commissioner of Patents PO Box 1450 Alexandria, VA 22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Ortho-McNeil Pharmaceutical, Inc.,("Ortho")Raritan, New Jersey, a New Jersey business corporation, owner of the above-identified patent by virtue of an Assignment executed on April 28, 1987 by Michael P. Wachter and Michael P. Ferro of their interests in the above-identified patent to Ortho Pharmaceutical Corporation, predecessor in name of Ortho-McNeil Pharmaceutical, Inc. and recorded in the United States Patent and Trademark Office ("USPTO") on April 29, 1987 at Reel 4699, Frame 0898 (Exhibit I), hereby requests an extension of the 20 year from filing date patent term of United States Patent No. 4,826,868.

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAMES, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is Zubrin™ Rapidly-Disintegrating Tablets (tepoxalin). As used herein, the chemical name for the active ingredient in the approved product is tepoxalin. The active ingredient in the approved product has the following structure and chemical names:

a. CHEMICAL STRUCTURAL FORMULA:

$$HO$$
 H_3C
 N
 CH_3

The following names and code numbers are synonymous and may be used interchangeably throughout the submission: International Non-

International Non-proprietary

Name (INN)/Generic Name: tepoxalin

US Adopted Name (USAN): tepoxalin

Other names: RWJ20485

SCH43208

ORF20485

CAS Registry Number: 103475-41-8

b. Chemical Names: (1). 3-[5-(4-chlorophenyl)-1-(4methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-propanamide;

(2). 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide; and (3). 5-(p-chlorophenyl)-1-(p-methoxyphenyl)-N-methylpyrazole-3-propionohydroxamic acid.

Molecular Formula: C₂₀H₂₀ClN₃O₃ Molecular Weight: 385.85g/mol

See INAD submission dated October 25, 1996 (Exhibit VI). On review, it was noted that the chemical name for tepoxalin is incorrect in the package insert. SPAH advises that they will correct same. (See package insert attached as part of Exhibit II).

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The regulatory review occurred under §512 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §360(b) Section 512 of FFDCA provides for the submission and approval of new animal drug applications ("NADAS") for animal drug products meeting the definition of "new animal drug" under §201(w) of the FFDCA.

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets was approved by the Center for Veterinary Medicine ("CVM") for commercial marketing on March 31, 2003 for the control of pain and inflammation associated with osteoarthritis in dogs (See Exhibit II).

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT,

A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT OR THE VIRUS-SERUM TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED.

The active ingredient in the approved product Zubrin™ Rapidly-Disintegrating Tablets has the USAN name of tepoxalin and the chemical names listed in Paragraph No.(1) hereinabove. The approved product Zubrin™ Rapidly-Disintegrating Tablets contains tepoxalin as the sole active ingredient which has not previously been approved by FDA for commercial marketing or use in animals under §512 of the FFDCA, or for use in humans under the FFDCA or under the Public Health Service Act or the Virus-Serum Toxin Act. (See Exhibit II)

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SEC. 1.720(F) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

The product was approved on March 31, 2003 and the last day within the sixty-day period permitted for submission of an application for extension of the relevant U.S. Patent is May 30, 2003. This application is being timely filed before the expiration May 30, 2003 deadline, pursuant to 35 USC §156(d)(1) and 37 CFR §1.740.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO. 4,826,868

INVENTORS: Michael P. Wachter and Michael P. Ferro

DATE OF ISSUE: May 2, 1989

FILING DATE: April 29,1987

CONTINUATION-IN-PART OF SERIAL NO. 867,996,

filed May 29, 1986.

EXPIRATION DATE: MAY 29, 2006

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS), AND DRAWINGS:

A copy of the U.S. Patent No. 4,826,868 is attached as Exhibit III.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

A copy of Terminal Disclaimer filed December 23, 1987 over copending application USSN 867,996, and now abandoned is attached as Exhibit IV.

No Certificate of Correction has issued for US Patent No. 4,826,868.

A copy of the maintenance fee statement indicating that the first maintenance fee was paid is attached hereto as Exhibit V.

United States Patent No. 4,826,868 has not been re-examined and as such no re-examination certificate has been issued.

- (9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT READS ON:
- (1) The approved product, if the listed claims include any claim to the approved product;
- U.S. Patent 4,826,868 claims the approved "product" in accordance with 37 CFR 1.710(b)(2).

Claim 2 of United States Patent No. 4,826,868 reads on Zubrin $^{\text{TM}}$ (tepoxalin) Rapidly-Disintegrating Tablets.

Claim 2 of United States Patent No. 4,826,868 reads:

2. A compound which is 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-propanamide.

The approved product, Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets contains tepoxalin as the active ingredient and is represented by the structural formula and chemical name set forth in paragraph 1 on page 2.

Thus, claim 2 covers tepoxalin, also known as 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-propanamide.

Thus, claim 2 reads on the approved product.

- (10) A STATEMENT BEGINNING ON A NEW PAGE, OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:
- (ii) FOR A PATENT CLAIMING A NEW ANIMAL DRUG: (A) THE DATE A MAJOR HEALTH OR ENVIRONMENTAL EFFECTS TEST ON THE DRUG WAS INITIATED AND ANY AVAILABLE SUBSTANTIATION OF THAT DATE, OR THE DATE OF AN EXEMPTION UNDER SUBSECTION (j) OF SECTION 512 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BECAME EFFECTIVE FOR SUCH ANIMAL DRUG; (B) THE DATE ON WHICH A NEW ANIMAL DRUG APPLICATION (NADA) WAS INITIALLY SUBMITTED AND THE NADA NUMBER; AND (C) THE DATE ON WHICH THE NADA WAS APPROVED;

INAD Number: 9916

INAD Effective Date: October 29, 1996

NADA Number: 141-193.

NADA Submission Date: December 20, 2001

NADA Approval Date: March 31, 2003

Ortho is the assignee of record of United States Patent No. 4,826,868 by virtue of an Assignment (executed on April 28, 1987) by Michael P. Wachter and Michael P. Ferro of their interests in the above-identified patent and recorded in the United States Patent and Trademark Office ("USPTO") on April 29, 1987 at Reel 4699, Frame 0898 (Exhibit I).

(i) SPAH on October 25, 1996 submitted to the FDA, a "Notice of Claimed Investigational Exemption for a New Animal Drug" (INAD) under §512 of the FFDCA for the purpose of demonstrating the effectiveness and safety of tepoxalin for inflammatory disorders in dogs. The letter transmitting the INAD to the FDA is attached as Exhibit VI. By a letter dated October 29, 1996, the Center for

Veterinary Medicine ("CVM") acknowledged receipt of the INAD and assigned the INAD No. 9916. A copy of this CVM letter is attached as Exhibit VII. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(4)(B)(i) as October 29, 1996, the effective date of an investigational exemption under §512.

- (ii) SPAH submitted a New Animal Drug Application (NADA) for Zubrin™ (tepoxalin) Tablets for dogs for the control of pain and inflammation associated with osteoarthritis on December 20, 2001. A copy of this letter transmitting the NADA is attached as Exhibit VIII. By a letter dated December 31, 2001, the CVM acknowledged receipt of the NADA submission dated [November (typographical error)] December 20,2001 and assigned the submission NADA No. 141-193. A copy of this CVM letter is attached as Exhibit IX.
- (iii) By a letter dated March 31, 2003 (copy attached as Exhibit II), the CVM advised SPAH that the NADA No. 141-193 dated December 20, 2001 (A 0000), as reactivated November 12, 2002 (E0009) and amended December 6, 2002 (T0011), January 3, 2003 (T0012) and January 24, 2003 (T0013) for use of Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets for the control of pain and inflammation associated with osteoarthritis in dogs was approved.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §156(g) (4) (B) (i), the "testing phase" began on October 29, 1996, the effective date of the INAD No. 9916 and ended December 20, 2001, the date the NADA No. 141-193 was initially submitted for use of Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets for the control of pain and inflammation associated with osteoarthritis in dogs under §512 of the FFDCA. For purposes of determining the "approval phase" of the "regulatory review period" under 35 U.S.C. §156(g) (4) (B) (ii) the "approval phase" began on December 20, 2001, the date the NADA No. 141-193 was initially submitted to the CVM and ended on

March 31, 2003, the date on which the NADA No. 141-193 was approved by the CVM.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY SCHERING-PLOUGH ANIMAL HEALTH, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

During the applicable regulatory review period, SPAH was actively involved in obtaining FDA approval for the use of tepoxalin for the control of pain and inflammation associated with osteoarthritis in dogs. As previously noted, SPAH submitted in INAD for the use of tepoxalin in dogs on October 25, 1996 and conducted clinical trials under INAD No. 9916. SPAH submitted NADA No. 141-193 for the use of tepoxalin for the control of pain and inflammation associated with osteoarthritis in dogs. December 20, 2001 SPAH continued to interact with various FDA officials and answered questions, and supplied requested information. A brief description of the significant activities undertaken by SPAH with respect to the use of tepoxalin for the control of pain and inflammation associated with osteoarthritis in dogs during the regulatory review period (INAD and NADA) is set forth in Exhibit X (A and B) that is illustrative of the activities involved.

SPAH acted with due diligence (1) under INAD No. 9916 during the "testing phase" of the regulatory review period under 35 U.S.C. §156(g)(40(B)(i), i.e., from October 29, 1996 to December 20, 2001 and (2) under NADA No. 141-193 during the "approval phase" of the regulatory review period under 35 U.S.C. §156(g)(4)(B)(ii), i.e., from December 20, 2001 to March 31, 2003.

Ortho reserves the right to present additional information in support of the conclusion that SPAH acted with due diligence during the regulatory review period. See, e.g., 21 C.F.R. §60.32.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR AN EXTENSION AND A STATEMENT AS TO THE LENGTH OF THE EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF THE EXTENSION WAS DETERMINED:

Extension of the 20 Year From Filing Term

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in the relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1);(3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 USC §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Publ. 103-465, 108 Stat. 4809 (1994) and 35 U.S.C. §156, the term of United States Patent No. 4,826,868 currently expires on May 29, 2006. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 4,826,868.

- (2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).
- (3) This application is being submitted by Ortho-McNeil Pharmaceutical, Inc., the owner of record of this patent through its agent. Ortho-McNeil Pharmaceutical, Inc. is the owner of record by virtue of an Assignment executed on April 28,1987 by Michael P. Wachter and Michael P. Ferro of their interests in the above-identified patent to Ortho Pharmaceutical Corporation predecessor in name of Ortho-McNeil Pharmaceutical, Inc. and recorded in USPTO on April 29,1987 at Reel 4699, Frame 0898 (Exhibit I). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on March 31, 2003 the date the product received permission for marketing under the FFDCA and ending on May 30, 2003 and contains the information required under 35 U.S.C. §156(d).
- (4) As evidenced by the March 31, 2003 letter to SPAH from the CVM (Exhibit II), the product was subject to a regulatory review period under §512(c) of the FFDCA before its commercial marketing or use.
- (5) Finally, Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets were approved for the control of pain and inflammation associated with osteoarthritis in dogs under §512 of FFDCA. The permission for the commercial marketing of the Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablet after regulatory review under §512 of FFDCA, is the first permitted commercial marketing and use under §512 for animals of the active ingredient tepoxalin in Zubrin™ (tepoxalin) Rapidly-Disintegrating Tablets. This is confirmed by the absence of any approved new animal drug application for the active ingredient in animals prior to March 31, 2003. See Exhibit II.
 - (b) Statement as to length of extension claimed:

The 20 year from filing term of United States Patent No. 4,826,868 now expiring on May 29, 2006 should be extended by 1405 days. This extension was determined on the following basis. As set forth in 35 U.S.C. §156(g)(4), the regulatory review period equals the length of time between the effective date of the INAD No. 9916 of October 29, 1996 and the submission of the NADA on December 20, 2001 a period of 1878 days, plus the length of time between the submission of the NADA on December 20, 2001 to NADA approval on March 31, 2003, a period of 466 days. These two periods added together equal 2344 days.

Pursuant to the introduction of 35 U.S.C. §156(c), the term of the patent eligible for extension shall be extended only for that portion of the regulatory review period which occurs after the date the patent is issued. In this case, the limitation under the introduction to §156(c) does not apply in that the issue date of United States Patent No. 4,826,868 (May 2, 1989) is before the date on which the regulatory review period began.

Section 156(c)(2), requires the period calculated under §156(g)(4)(B)(i) to be reduced by one-half of the 1878 day period; this reduction results in a period of 939 days.

From the foregoing calculation, an extension of 1405 days results, i.e., the period under 35 U.S.C. 156(g)(4)(B)(i) (939 days) plus the period under 35 U.S.C. 156(g)(4)(B)(ii) (466 days).

Pursuant to 35 U.S.C. §156(g)(6)(A), the period of extension determined under any of the preceding paragraphs may not exceed five (5) years if the patent involved was issued after the date of enactment of this section.

The instant patent, U.S. Patent No. 4,826,868 was issued on May 2, 1989, which is a date after the November 16, 1988 date of enactment of 35 U.S.C. §156(g)(6)(C).

Under 35 U.S.C. §156(c)(3), if the period remaining in the term of the patent after the date of approval, that is, March 31, 2003 to May 29, 2006, when added to the extension period calculated above exceeds 14 years, the period of extension must be limited so that the total does not exceed 14 years. In this case, the total of the remaining term (1155 days) plus the calculated extension (1405 days) does not exceed the 14-year (5113 days) limit, therefore, the 14 years limitation does not apply.

Accordingly, Ortho asserts that USP 4,826,868 is eligible for a 1405 day extension from May 29, 2006 to April 3, 2010.

(13) A STATEMENT ON A NEW PAGE THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT.

Ortho acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) PRESCRIBED FEES:

The Commissioner is authorized to charge our Deposit Account No. 10-0750/ORT-518/EGC in the amount of \$1,120.00 or any other fee necessary for this application to prevent it from becoming inadvertently abandoned. Duplicate copies of these pages are enclosed.

(15) THE NAME, ADDRESS AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THIS APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED TO:

ADDRESS: Philip S. Johnson, Esq.

JOHNSON & JOHNSON

ONE JOHNSON & JOHNSON PLAZA

NEW BRUNSWICK, NEW JERSEY 08933-7003

CALLS: ELLEN CIAMBRONE COLETTI, ESQ.

(732)524-2359

(b) CERTIFICATION THAT THE ENCLOSED DUPLICATE COPIES OF THIS APPLICATION ARE TRUE COPIES OF THE ORIGINAL:

CERTIFICATION

I, Ellen Ciambrone Coletti, Registration No. 34,140, as attorney for Applicant, Ortho-McNeil Pharmaceutical, Inc., owner of record of United States Patent No. 4,826,868 (by virtue of the aforesaid Assignment to Ortho Pharmaceutical Corporation predecessor in name of Ortho-McNeil Pharmaceutical, Inc., Exhibit I) which has applied for an extension of term of this patent,

hereby certify that the two copies of this application transmitted herewith are true copies of the original application.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of United States Patent No. 4,826,868.

Date: 5-28-03

Ellen Ciambrone Coletti Attorney for Applicant Registration No. 34,140 Tel. No. (732)524-2359

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
Patent Department
New Brunswick, New Jersey 08933-2359

DECLARATION FOR EXTENSION OF UNITED STATES PATENT NO. 4,826,868

I, Ellen Ciambrone Coletti, Registration No. 34,140, declare the following: that I am a patent attorney authorized to practice before the United States Patent and Trademark Office and have general authority to act in patent matters before the United States Patent and Trademark Office on behalf of Ortho-McNeil Pharmaceutical, Inc. ("Ortho"), owner of the above-identified patent by virtue of the aforesaid Assignment to Ortho Pharmaceutical Corporation predecessor in name of Ortho-McNeil Pharmaceutical, Inc. (Exhibit I), which has applied for an extension of term of this patent; that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,826,868; that I believe that the patent is subject to extension under 35 U.S.C. §156; that I believe that the length of extension claimed is justified under 35 U.S.C. §156, and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may

jeopardize the validity of this application and any extension of United States Patent No. 4,826,868.

Date: 5-28-03

Ellen Ciambrone Coletti Attorney for Applicant Registration No. 34,140 Tel. No. (732)524-2359

Johnson & Johnson One Johnson & Johnson Plaza Patent Department New Brunswick, New Jersey 08933-2359

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wachter et al.

Serial No. : 07/042661 Art Unit: 121

Filed: April 29, 1987 Examiner: R. Ramsuer

For : 1,5-Diaryl-3-Substituted Pyrazoles

Pharmaceutical Compositions and Use

Commissioner for Patents Washington, D.C. 20231

ASSOCIATE POWER OF ATTORNEY

Sir:

In the matter of the above-identified application, I hereby appoint Ellen Ciambrone Coletti (Reg. No. 34,140), whose postal address is One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933-7003, my associate attorney to prosecute said application, to make alterations and amendments therein, to file continuing applications claiming the benefit of said application, to receive the patent and to transact all business in the Patent Office connected with said application.

I request all communications with respect to said application be addressed to Philip S. Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933-7003. All telephone calls should be directed to Ellen Ciambrone Coletti (732) 524-2359.

Signed at New Brunswick, in the County of Middlesex and State of New Jersey, this 28th day of May, 2003.

Steven P. Berman Reg. No. 24,772

Attorney for Applicant(s)

One Johnson & Johnson Plaza New Brunswick, NJ 08933-7003 (732) 524-2805

DATED: May 28, 2003

Exhibit

11-1

erial No.

WHEREAS, Michael Paul Wachter and Michael Paul Perro, citizens of the United States of America, residing at 52 North Street, P.O. Box 362, Bloomsbury, NJ 08804 and 161 Woods Road, Somerville, NJ 08876 (hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

PHARMACOLOGICALLY ACTIVE 1.5-DIARYL-3-SUBSTITUTED-PYRAZOLES AND METHOD FOR SYNTHESIZING THE SAME

for which they have this day executed an application for Letters Patent of the United States; and

WHEREAS, ORTHO PHARMACEUTICAL CORPORATION, corporation of the State of New Jersey, (hereinafter called "Assignee"), is desirous of acquiring Assignors' entire right, title, and interest therein:

NOW. THEREFORE, BE IT KNOWN that for and in consideration of the sum of One Dollar and other valuable considerations to them moving, the receipt of which is hereby acknowledged, Assignors have sold, assigned, and transferred, and do hereby sell, assign and transfer unto said Assignee their entire right, title and interest in and to all said inventions and discoveries disclosed in said application whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, divisions, and continuations thereof, and in and to all Letters Patent. United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid. Assignors covenant and agree with said Assignee that he has a full and unencumbered title to the inventions and discoveries above described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns:

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection test the said inventions and discoveries or that may be necessary to discoveries and patents hereby conveyed and to enable it to record said title.

TN TESTIMONY this 28	WHEREOF, Assignors have hereunto set their hands day of April . 1987.
	Michael Paul Wachter (L.S.)
	Michael Paul Ferro (L.S.)

TATE OF NEW JERSEY

,) 88.

COUNTY OF SOMERSET

BE IT REMEMBERED. That on this day of day of

Notary Public

PAULA FOJTLIN

NOTARY PUBLIC OF NEW JERSEY
My Commission Expires May 29, 1991

APR 20 1987

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RECEIVED

Food and Drug Administration Rockville MD 20857

APR 0 7 2003

NADA 141-193 E0009

REGULATORY AFFAIRS

MAR 3 1 2003

Schering-Plough Animal Health Corporation Attention: Diane deBruin, B.Sc., MBA 1095 Morris Avenue PO Box 3182 Union, NJ 07083

Dear Ms. deBruin:

We refer to your original New Animal Drug Application (NADA) dated December 20, 2001 (A0000), as reactivated November 12, 2002 (E0009) and amended December 6, 2002 (T0011), January 3, 2003 (T0012), and January 24, 2003 (T0013) for ZUBRINTM (tepoxalin) Rapidly-Disintegrating Tablets. The drug is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. Prior to distribution and marketing, three copies of each component of the final printed labeling must be submitted to CVM. All labeling should be identical to the facsimile labeling submitted on January 24, 2003 (T0013).

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

Manufacturing process validation is required under GMPs (21 CFR Parts 211 and 226). A product that does not conform to GMPs is adulterated (21 USC 351(a)(1)(B)). If manufacturing process validation information was not available or was found deficient at the time of the pre-approval inspection, the appropriate FDA District Office should be contacted after such validation has been completed on production lots and prior to shipment of the drug product. FDA may take regulatory action if drug products are shipped prior to completion of the validation process.

An expiration dating of 24 months is acceptable for this product.

If you submit any correspondence in the future relating to this approval, you should include a citation to this letter by date and NADA number. Any request to change the conditions of approval may require the submission of a supplemental application. If you have any questions, please contact Dr. Melanie Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely yours,

Stephen F. Sundlof, D.V.M., Ph.D.

Director, Center for Veterinary Medicine

Enclosure: FOI Summary

FREEDOM OF INFORMATION SUMMARY

NADA # 141-193

ZUBRINTM

Tepoxalin

Rapidly-Disintegrating Tablets

For Dogs

" for the control of pain and inflammation associated with osteoarthritis."

SCHERING-PLOUGH ANIMAL HEALTH 1095 Morris Ave. P.O. Box 3182 Union, N.J. 07083-1982

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

NADA Number: 141-193

Sponsor: Schering-Plough Animal Health Corporation

1095 Morris Ave. Union, N.J. 07083

Drug Labeler Code: 000061

Established Name: tepoxalin

Proprietary Name: ZUBRIN™ Rapidly-Disintegrating Tablets

Dosage Form: Oral tablets: ZUBRINTM is available as white, circular,

freeze-dried, rapidly- disintegrating tablets which, when administered orally, disintegrate within seconds after placement in the mouth, thus allowing the contents to be

swallowed.

How Supplied: ZUBRINTM Tablets are supplied in boxes containing 10 foil

blisters each. Each foil blister contains 10 rapidly-

disintegrating tablets of 30, 50, 100, or 200 mg tepoxalin.

How Dispensed: Rx - Federal law restricts this drug to use by or on the order

of a licensed veterinarian.

Amount of Active

Ingredient: Each rapidly- disintegrating tablet contains 30, 50, 100, or

200 mg tepoxalin.

Route of

Administration: Oral

Species/Class: Dogs/Canine

Recommended

Dosage: Dosage: Administer 10 mg/kg (4.5 mg/lb) or 20 mg/kg

(9.1 mg/lb) on the initial day of treatment, followed by a daily maintenance dose of 10 mg/kg. Due to observed variability in tepoxalin metabolism, a higher initial dose of 20 mg/kg may be given to increase the likelihood that plasma active metabolite levels will reach a minimum

effective concentration following the first oral

administration. This could be beneficial to dogs that show signs of severe osteoarthritic pain. The duration of treatment at 10 mg/kg should be based on clinical response and patient tolerance of drug treatment.

Administration: Place the rapidly-disintegrating tablet into the dog's mouth. Keep the mouth closed for a sufficient amount of time (~4 seconds) to ensure tablet dispersion. ZUBRINTM Tablets should be administered either with food or within 1 to 2 hours after feeding.

Due to tablet sizes, dogs weighing less than 3 kg (6.6 lbs) cannot be accurately dosed.

Pharmacological

Category:

Non-steroidal Anti-inflammatory Drug

Indications:

ZUBRINTM (tepoxalin) Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

2. EFFECTIVENESS:

a. Dosage Characterization:

(1) 10 mg/kg maintenance dose:

A multiple site field study (Study No. E99-473) was conducted in the United States to assess the dose response control of dogs with osteoarthritis when tepoxalin was administered using three different doses of ZUBRINTM Tablets.

Fifty-two dogs with clinical signs attributable to osteoarthritis presented to veterinarians, and were randomly allocated to treatment with ZUBRINTM at one of 3 doses (5.0 mg/kg, 7.5 mg/kg, and 10.0 mg/kg) for 7 consecutive days. Ease of ambulation, weight bearing, pain and resistance to palpation, pain and resistance to forced movement, and general attitude and demeanor were evaluated. The most effective dose among the three dose groups was 10 mg/kg. Sixteen dogs received 10 mg/kg tepoxalin on the initial day of therapy and for 6 additional consecutive days. Of these 16 dogs, 14 showed improvement in clinical signs related to osteoarthritis after 7 days of therapy at 10 mg/kg.

(2) 20 mg/kg initial day dose:

A study was conducted to determine the pharmacokinetic profile of tepoxalin administered orally to 12 dogs at an initial dose of 20 mg/kg, followed by a dose of 10 mg/kg once daily for six additional days (Study No. N00-576).

Results: Mean tepoxalin pharmacokinetic parameters in dogs (± standard deviation).

		T _{max} (hr)	C _{max} (ng/mL)	T _{1/2} (hr)	AUC ₀₋₂₄ * (hr*ng/mL)
	Day 0	$2.3 \pm 1.4**$	780 ± 506	2.0 ± 1.2	3363 ± 1841
Tepoxalin	Day 1	2.3 ± 1.9	529 ± 182	2.3 ± 1.4	2324 ± 1394
	Day 6	2.8 ± 4.2	637 ± 317	1.6 ± 0.6	2434 ± 1499
	Day 0	4.7 ± 6.2	831 ± 357	13.7 ± 10.7	8460 ± 3527
Active Metabolite	Day 1	2.7 ± 1.9	986 ± 323	12.4 ± 8.4	11297 ± 5728
Mictabolite	Day 6	6.8 ± 8.0	968 ± 486	13.4 ± 10.3	12094 ± 8195

^{*} Where AUC represents the area under the concentration/time curve over either one complete dosing interval (active metabolite) or to the last quantifiable concentration (tepoxalin).

Tepoxalin is rapidly absorbed after oral administration. Its half-life in plasma is short due to conversion to an active metabolite. The active metabolite has a long half-life which justifies once daily dosing of ZUBRINTM Tablets. Clinical signs of toxicity, as demonstrated in safety studies, were dose related rather than related to the duration of dosing (see SAFETY section).

Substantial intrasubject and intersubject variability was associated with the pharmacokinetics of tepoxalin. As a result of these highly variable kinetics, it is recommended that when time to onset of pain relief is critical, therapy be initiated at a dose rate of 20 mg/kg to improve the likelihood that systemic drug concentrations rapidly and consistently exceed the minimum effective concentration of this compound and its active metabolite.

b. SUBSTANTIAL EVIDENCE (field study):

A controlled field study was conducted in dogs using the dosage of 20 mg/kg for one day, followed by 10 mg/kg daily for an additional 6 days. Tepoxalin was administered for one week to demonstrate the effectiveness and safety of tepoxalin tablets for the control of pain and inflammation associated with osteoarthritis.

ZUBRIN™ (tepoxalin) field study at small animal clinics in the US (Study No. 1930C-61-V98-372, Report No. 30116)

- (1) Type of Study: Multi-Centered Controlled Field Study
- (2) Investigators:

^{**}standard deviation

Investigator	Investigator
Andrew Pickering, DVM	Todd Schadler, DVM
Wabash Valley Animal Hospital	Great Southern Animal Hospital
3004 S. 7 th Street	2685 South High Street
Terre Haute, IN 47802	Columbus, OH 43207
Roger Sifferman, DVM	L. D. Eckermann, DVM
Bradford Park Veterinary Hospital	Westbury Animal Hospital
1255 East Independence	4917 South Willow Drive
Springfield, MI 65804	Houston, TX 77035
K. S. Griffin, DVM	Richard Benjamin, DVM
W. Van Hooser, DVM	Berkeley Dog & Cat Hospital
Carriage Hills Animal Clinic	2126 Haste Street
3200 Eastern Bypass	Berkeley, CA 94704
Montgomery, AL 36116	
Robert Yelland, DVM	Donald Copeland, DVM
Lewelling Veterinary Clinic	Bellaire Richmond Animal Hospital
525 Lewelling Boulevard	5808 Bissonnet
San Leandro, CA 94579	Houston, TX 77081-6599
Jack W. Whitmore, DVM	Ben Garrett, DVM
Stuebner Airline/Champions Veterinary	Garrett Veterinary Hospital
Hospital	1846 South Oates
16116 Stuebner Airline	Dothan, AL 36301
Spring, TX 77379	

(3) General Design:

- (a) Purpose: The objective of the study was to evaluate, under field conditions, the effectiveness and safety of ZUBRINTM for the control of pain and inflammation associated with canine osteoarthritis.
- (b) Animals: Two-hundred and five dogs were evaluated for safety and 122 (62 tepoxalin and 60 carprofen) were evaluated for effectiveness. The mean age of dogs was 8.1 years (4 months 18 years).
- (c) Control: The active control product was an approved carprofen tablet.
- (d) Diagnosis: The diagnosis of osteoarthritis was based on medical history and physical examination, including radiography, and included cases of hip dysplasia, osteoarthritis and discospondylosis.
- (e) Dosage Form: ZUBRIN™ (tepoxalin) rapidly-disintegrating tablet containing 50 or 200 mg of tepoxalin
- (f) Route of Administration: Oral
- (g) Dosages used:

Active control: 2.2 mg carprofen/kg twice daily for seven days. Tepoxalin: 20 mg tepoxalin/kg on the first day followed by 10 mg/kg daily for six consecutive days.

- (h) Test Duration: 7 days
- (i) Parameters Measured on Day 0 and Day 6:
 - Ease of ambulation/locomotion
 - Weight bearing
 - Pain and resistance to palpation
 - Pain and resistance to forced movement
 - General attitude
 - An overall (general) evaluation was made on Day 6 by both the owner and the investigator. Animals were classified as "vastly improved", "improved", "no change" or "worse".
- (4) Results: Results of the study showed statistically significant improvement for all parameters comparing Day 0 to Day 6 within the tepoxalin group.

Tepoxalin and Carprofen: Number Affected for Clinical Parameters of Osteoarthritis in Dogs

Parameter	Ease of Ambulation & Locomotion		Weight Bearing				Pain & Resistance to Forced Movement	
	(n=62)	(n=60)	T (n=62)	C (n=60)	T = 62)	C (n=60)	T (n=82)	C (n=60)
Day 0	3. 特别·芬	1. 化清晰		ng ra				Herrican Company
Normal	1	2	6	6	4	5	0 .	2
Slight	18	20	23	26	20	14	19	13
Moderate	30	26	25	23	26	31	31	28
Severe	13	12	7	5	12	10	12	17
Day 6		*	N. 49.2				enserge de la companya de la company	and the second
Normal	27	27	37	36	26	31	25	25
Slight	33	25	20	17	31	23	30	28
Moderate	3	7	5	6	5	5	7	6
Severe	0	1	0	1	0	1	0	1

T = Tepoxalin; C = Carprofen

Tepoxalin and Carprofen: Number Affected for General Attitude

General :	Tepoxalin	(n=62) 342 44314	M. Chipioter		
Attitude	Day 0	Day 654	PER DIVIDE	Day 6 Parks	
% Normal	37	59	35	55	
% Modified	25	3	25	5	

Tepoxalin and Carprofen: Effectiveness for Investigator and Owner Evaluation

Parmeer # (Day())	ireament Group	Anity alimitated (D) 2 + 5 2	improyal _{is} s (0) ^E essae &	Noterings 3
Investigator	Tepoxalin (n=62)	22	37	3
Evaluation	Carprofen (n=60)	18	36	6
Owner	Tepoxalin (n=62)	20	38	4
Evaluation	Carprofen (n=60)	26	29	4

(5) Statistical analysis: After removing dogs that were normal on both days 0 and 6, scores for each endpoint were converted to a recording of "success" if the dog experienced a decrease of at least one score between day 0 and day 6, otherwise the dog was considered to have "failed" with respect to that endpoint. Ninety percent exact confidence intervals for the difference in the proportion of dogs scored as successes for each treatment were constructed. The lower bound of the confidence interval is taken as an estimate of the maximal negative difference in effectiveness for tepoxalin compared to the active control drug. Based on the estimated maximal differences, tepoxalin was considered noninferior to the comparator product. The success rates for the comparator product and the estimated maximal differences are displayed in the following table.

Estimated maximal differences between the success rates for tepoxalin and the comparator drug carprofen for each endpoint.

	ૢ૽ૹઌ૽૽૽૽ૺઌ૾ૺૡ૽૽૽૽૿ૺ૱ઌૡ૿ૢ		
	ini Ceroviden (Comparitor)		
	Group (xtotal)	Contraction of	
Ease of ambulation/locomotion	81% (47 of 58)	92% (56 of 61)	-2.5%
Weight Bearing	80% (43 of 54)	84% (46 of 55)	-11.4%
Pain on Palpation	87% (48 of 55)	86% (50 of 58)	-17.6%
Pain on Forced Movement	81% (48 of 59)	82% (51 of 62)	-13.1%
Investigator Evaluation	90% (54 of 60)	95% (59 of 62)	-6.6%
Owner Evaluation	92% (55 of 60)	94% (58 of 62)	-10.0%
General Attitude	80% (20 of 25)	88% (22 of 25)	-16.3%

(6) Conclusion: Under the conditions of this study, ZUBRINTM Tablets administered orally at a dosage of 20 mg/kg once on the first day, followed by a dose of 10 mg/kg administered once daily for six consecutive days, were shown to be safe

and effective for the control of pain and inflammation associated with canine osteoarthritis.

(7) Adverse Reactions:

The following table lists the adverse reactions that were observed during the field study (dogs received either ZUBRINTM Tablets or carprofen for 7 days):

Nilword Egyptini	Samile in august werely of the Valley of the Company of the Valley of the Company	A reflect of any reserve rate.
Vomition	2	5
Diarrhea	4	0
Anorexia	0	1
Ineffectiveness	0	1
Incoordination	1	0
Death**	1	-

^{*}Dogs may have experienced more than one of the observations during the study.

3. TARGET ANIMAL SAFETY:

Two laboratory studies were conducted to evaluate the safety of tepoxalin when administered orally to dogs. A 26-week oral toxicity study (with an interim 13-week sacrifice) and a 1-year oral toxicity study provided safety data. In a third study, field safety was evaluated in 107 dogs receiving 28 consecutive days of ZUBRINTM Tablet therapy in an uncontrolled field study.

The laboratory studies were conducted with drug substance suspended in hydroxypropylmethylcellulose and administered to dogs by gavage in split dosing (twice daily, given 4-5 hours apart) to maximize oral bioavailability. Bioavailability data was used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation.

a. Twenty-Six Week Oral Toxicity Study of Tepoxalin in Dogs (13-week interim report) (Study No. 21121:01:00, Report Numbers A-27657 & A-27658)

- (1) Type of Study: 26-week oral toxicity study with a thirteen-week interim necropsy (The study was conducted in compliance with FDA's Good Laboratory Practices Regulations for Nonclinical Laboratory Studies (21 CFR Part 58).
- (2) Study Director: Dr. E.V. Knight

The R.W. Johnson Pharmaceutical Research Institute

PRI Research Farm

^{**}Two days after the completion of the field study, one nine-year-old Labrador retriever became seriously ill and subsequently died. Necropsy results showed multiple gastric ulcerations (3-8 mm), anemia, and severe diffuse gastroenteritis. The dog's death could not be definitively attributed to the administration of tepoxalin.

Pittstown, NJ

- (3) General Design:
 - (a) Purpose: To assess the toxicity of tepoxalin when administered orally to Beagle dogs for twenty-six weeks with a thirteen-week interim necropsy.
 - (b) Test Animals: Fifty-six Beagle dogs were assigned to four groups (7/sex/group). An interim sacrifice of 3 dogs/sex/group was conducted after 13 weeks of dosing. Animals were seven months of age at the time of initiation of dosing.
 - (c) Dosage Form: Tepoxalin micronized suspension at concentrations of 10 and 150 mg/mL (Bioavailability data was used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation.)
 - (d) Placebo Control: 0.5% Hydroxypropyl Methylcellulose Premium F4M
 - (e) Doses Used:

Doses Used in Study No. 21121:01:00/Report Numbers A-27658 and A-27657

Total Dose* (mg/kg/day)	Relative Dose**
0	0X
20	1-2X
100	10-20X
300	15-30X

^{*}Total treatment dose was divided and administered twice daily.

- (f) Route of Administration: Oral gavage
- (g) Treatment Duration: Twenty-six weeks (with thirteen week interim sacrifice)
- (h) Parameters Measured:
 - <u>1</u> Clinical Observations
 - 2 Physical Examination
 - 3 Food Consumption
 - 4 Body Weight

^{**}Relative dose refers to multiples of the recommended therapeutic dose of 20 mg/kg as a one-time induction dose, followed by a maintenance dose of 10 mg/kg.

- <u>5</u> Mortality Check
- Ophthalmoscopic Examination
- Electrocardiographic Analysis
- 7 8 9 Hematology
- Coagulation
- <u>10</u> **Blood Chemistry**
- 11 Urinalysis
- **Gross Pathology** 12
- Organ Weights 13
- 14 Histopathology

(4) Results:

13 week findings:

There were no drug-related changes in body weight gain, food consumption, clinical signs, or results of ophthalmologic examinations. Discolored feces ranging from white to yellowish tan were noted mainly in dogs receiving doses of 100 and 300 mg/kg/day. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract. No drug-related changes were observed in the clinical pathology parameters for the 20 and 100 mg/kg/day dosage groups. At weeks 6 and 14, one female dog in the 300 mg/kg/day group showed neutrophilic leukocytosis, decreased RBC, Hb and PCV, decreased serum total protein, decreased albumin, and decreased calcium (later confirmed to be a result of chronic gastric ulceration at the week 27 necropsy). The clinical pathology changes were attributed to the administration of tepoxalin. Two other females (20 mg and 100 mg groups) showed mild to moderate RBC, Hb and PCV decreases at week 14 that returned to predosage levels by week 27. These changes were considered possibly related to tepoxalin.

At 13 weeks, 6 dogs per treatment group were necropsied. Dogs in all dosage groups showed evidence of gastric irritation (mucosal hemorrhage and congestion) after 13 weeks: 1 in the 0 mg/kg dose group, 1 in the 20 mg/kg dose group, 3 in the 100 mg/kg group, and 2 dogs in the 300 mg/kg group. One of the 2 dogs that received the highest dose (300 mg/kg) showed gastric ulceration at the mid-study necropsy. The ulcers were confirmed histologically and attributed to the administration of tepoxalin.

26 week findings:

There were no drug-related changes in body weight gain, food consumption, clinical signs, or results of ophthalmologic examinations. Discolored feces ranging from white to yellowish tan were noted mainly in dogs receiving doses of 100 and 300 mg/kg/day. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract.

In the 20 mg/kg/day dosage group, one female dog showed RBC, Hb and PCV decreases at week 14 that returned to predosage levels by week 27. By the final week of the study, two female dogs in the 300 mg/kg/day dose group had decreased RBC, Hb, and PCV values; as well as increased WBC and neutrophil counts in one of these females at week 27

At 26 weeks, the remaining 8 dogs per group were necropsied. Necropsy results demonstrated gross gastric lesions in no dogs in the 0 mg/kg/day group, one dog in the 20 mg/kg/day group, two dogs in the 100 mg/kg/day group, and four dogs in the 300 mg/kg/day group. Gastric ulceration was confirmed by histopathology in the highest dose group (300 mg/kg/day) in 2 of the 4 dogs with gross gastrointestinal abnormalities. Dogs in the lower dose groups showed evidence of gastric irritation (mucosal hemorrhage and congestion) after 6 months treatment with tepoxalin.

(6) Conclusions:

Adverse reactions were dose related and resulted in gastric ulceration (with associated clinical pathology changes) in the high dose group (300 mg/kg/day). Abnormalities of the gastrointestinal tract (enteritis, mild mucosal hemorrhage and congestion) were noted in all dosage groups.

- One-Year Oral Toxicity Study for Tepoxalin in Beagle Dogs (Study No. 92018, Report No. A-30023)
 - (1) Type of Study: One-year oral toxicity (The study was conducted in compliance with FDA's Good Laboratory Practices Regulations for Nonclinical Laboratory Studies, 21 CFR Part 58).
 - (2) Study Director:

Dr. E.V. Knight
The R.W. Johnson Pharmaceutical Research Institute
Route 202
Raritan, NJ

- (3) General Design:
 - (a) Purpose: To assess the toxicity of tepoxalin when administered orally to Beagle dogs for fifty-two weeks
 - (b) Test Animals: Thirty-two Beagle dogs were assigned to four groups (4/sex/group). Animals were eight months of age at the time of initiation of dosing.

- (c) Dosage Form: Tepoxalin micronized suspension at concentrations of 5, 15 and 50 mg/mL (Bioavailability data were used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation).
- (d) Placebo Control: 0.5% Hydroxypropyl Methylcellulose Premium F4M
- (e) Doses Used:

Doses Used in Study No. 92018/Report No. A-30023

Total Dose* (mg/	kg/day)
0	0X
10	0.5-1X
30	1.5-3X
100	5-10X

^{*}Total treatment dose was divided and administered twice daily.

- **(f)** Route of Administration: Oral gavage
- (g) Treatment Duration: Fifty-two weeks
- (h) Parameters Measured:
 - 1 Clinical Observations
 - Physical Examination
 - Food Consumption
 - **Body Weight**
 - Ophthalmoscopic Examination
 - Electrocardiographic Analysis
 - Hematology
 - Coagulation
 - 23456789 **Blood Chemistry**
 - 10 Urinalysis
 - **Gross Pathology** 11
 - Organ Weights 12
 - 13 Histopathology
- (4) Results:

Pale yellow to white material was frequently observed in the feces of tepoxalin treated dogs. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract. Treatment related macroscopic

^{**}Relative dose refers to multiples of the recommended therapeutic dose of 20 mg/kg as a one-time induction dose, followed by a maintenance dose of 10 mg/kg.

red and/or depressed foci were noted in the pyloric mucosa of the stomach of two female dogs in the 100 mg/kg/day dosage group. These changes were confirmed on histopathological evaluation as gastric erosion and ulceration. Gastric mucosal hemorrhage was noted in a third dog in this dosage group. No treatment-related microscopic changes were observed in the stomach of any dogs in the 10 or 30 mg/kg/day dosage groups.

Emesis occurred more frequently in the 100 mg/kg/day dogs:

Type of vomiting	Dosage group	Number of dogs*
food vomiting	10 mg/kg/day	2
foamy vomiting	30 mg/kg/day	1
_	100 mg/kg/day	2
discolored vomiting	100 mg/kg/day	3
drug vomiting	100 mg/kg/day	• 1
mucoid vomiting	100 mg/kg/day	2

^{*}Dogs listed may have vomited more than once

(6) Conclusions:

The study confirmed the occurrence of gastrointestinal abnormalities when tepoxalin is administered at exaggerated dosages. In the healthy dogs used in this study, an adequate safety margin existed for the oral treatment of dogs with tepoxalin at the recommended maintenance dose of 10 mg/kg/day.

c. ZUBRIN™ (tepoxalin) European field study 439: Safety of ZUBRIN™ tablets, administered orally for 28 days, for the control of pain and inflammation associated with osteoarthritis in dogs

(1) Study Dates: June to December, 1999

(2) Investigators:

Investigator.	Address
Dr. H. Maltot	Clinique Veterinaire de Senlis
	12-14 Place des Arenes, 60300 Senlis – France
Dr. L. Kern	Clinique Veterinaire
	4 rue Meissonier, 75017 Paris – France
Dr. F. Miguet	Clinique Veterinaire de Fleurie
	Place de l'Eglise, 69820 Fleurie – France
Drs. Schwarz & Winzinger	Georgenstrasse 22b
	D-82152 Planegg – Germany
Dr. Kendlinger	Moltkestrasse 2
	D-84453 Mühldorf – Germany

- (3) Study Design: An open (uncontrolled, unmasked) study with a total of 107 dogs enrolled at 5 sites.
- (4) Purpose of Study: The study demonstrates the field safety of tepoxalin rapidly-disintegrating tablets (market formulation) administered orally for 28 days for the control of pain and inflammation associated with osteoarthritis (OA) in dogs.
- (5) Description of test animals: A total of 107 dogs were enrolled in this study by 5 investigators (9 to 29 dogs per clinic). All 107 enrolled dogs were used in the safety evaluation.
- (6) Control group: none
- (7) Treatment group: Tepoxalin rapidly-disintegrating tablets (market formulation) were administered to all dogs included in the study.
- (8) Inclusion criteria: Dogs of various breeds, ages, sex and weights exhibiting pain and/or inflammation from an arthritic condition were candidates for this field study.
- (9) Exclusion criteria: Pregnant dogs or dogs specifically destined for reproduction were not enrolled in this study. Dogs which had received analgesic, antipyretic or antiinflammatory drugs (corticosteroids, NSAIDs) within the previous 5 days were excluded from this study. Post-surgical cases were excluded from this study.
- (10) Owner consent: Consent of the owner was obtained before any dog was included in the study.
- Osage form: Tepoxalin's market formulation is a white, circular, freezedried, fast-dissolving tablet that disintegrates in approximately four seconds after placement in the mouth. The test article consisted of 3 different sizes of ZUBRINTM Tablets containing 50, 100 or 200 mg of tepoxalin.
- (12) Drug dosage, frequency, duration and route of administration: The tepoxalin dosage was 20 mg/kg orally on day 0, followed by 10 mg/kg from day 0-27.
- (13) Relationship to feeding: within an hour after feeding
- (14) Study parameters:

Physical examination: On Day 0, a medical history of the case was taken, including an evaluation of the general physical condition, a description of

significant findings which may impact overall health or progression of the healing process, and a list of concurrent treatments. Osteoarthritis was confirmed by radiography. The dogs returned to the clinic on Day 13 and again after completion of the treatment period.

Clinical pathology: On Day 0, Day 13 and Day 27, a blood sample was drawn for CBC. Blood chemistry profiles (ALT, AST, GGT, ALP, TP, CK, albumin, urea, creatinine, Ca, P, Na, K, Cl) were established on Day 0 and Day 27.

Adverse reactions: The dogs were also observed daily by the owner for adverse reactions.

(15) Results:

Demographics:

Dogs of 34 different breeds or mixed breeds were represented in this study. The following table shows that, in general, older dogs tended to enroll for the control of OA pain:

Site number	Mean age (years)	Minimum age (years)	Maximum age - (years)
1	9.8	2	. 13.3
2	9.2	2.5	14
3	10.7	. 2.9	15
4	10.2	3	17.3
5	9.3	1.2	17.3

Clinical Pathology:

Hematology parameters were measured pretreatment, at Day 13 and Day 27. The proportion of dogs with a "normal" PCV fell below 80% (77.2%) at the second visit and went back up over 80% at the last visit. Only 2 cases with low PCV at the interim visit exhibited diarrhea and/or vomiting at some point during the study.

Serum chemistry parameters were measured pretreatment, at Day 13 and Day 27. One dog showed elevated ALT at the last visit (>200 IU/L). Three dogs had highly elevated BUN (>100 mg/dL) associated with increased creatinine. One case had highly elevated BUN and creatinine on Day 0 (pretreatment: 231 mg/dL and 3.4 mg/dL, respectively) and Day 6 (3 days after treatment termination: 143 mg/dl and 3.6 mg/dL, respectively). Another case had highly elevated BUN and creatinine on Day 0 (pretreatment: 165 mg/dL and 3.2 mg/dL, respectively) and at the end of the study (post treatment termination: 182 mg/dL and 3.4 mg/dL, respectively). These were also associated with low PCV, RBC, and hemoglobin. A third case had highly elevated BUN (>100 mg/dL) and slightly elevated

creatinine on Day 0; post treatment biochemistry results were not available for this dog.

Adverse Reactions:

Of the 107 dogs enrolled and used in the safety analysis, 97 (90.7%) completed the 28 day course of therapy. Of the 10 dogs that discontinued therapy before the completion of the study, 7 were related to adverse events (see below). The most commonly reported adverse reaction was gastrointestinal (GI) upset which was manifested by at least one of the following: diarrhea, vomiting, loss of appetite, soft feces, and enteritis. Other adverse reactions which may be related to GI upset include: fatigue/lethargy, flatulence, and eating grass.

Adverse reactions observed in dogs that participated in an uncontrolled field study treated with ZUBRINTM Tablets for 28 days

Adverse Reaction	Number of Dogs* (n= 107)	Median Number of Days Observed (Range)
diarrhea	23	2 days (1 to 31)
vomiting	21	1 day (1 to 8)
anorexia/inappetance	9	3 days (1 to 15)
enteritis	4	3 days (1 to 5)
lethargy	3	3 days (2 to 15)
flatulence	1	31 days
trembling	1	27 days
increase appetite	1	2 days
eating grass	1	3 days
incontinence	1	3 days
hair loss	1	5 days
death	1**	

^{*}dogs may have experienced more than one of the observations during the study.

Eight dogs exhibited both vomiting and diarrhea, but only five dogs exhibited both signs simultaneously.

Hematology results indicated that detectable blood loss occurred in three of the cases that were reported with diarrhea or vomiting. Two of the three cases had slightly lower PCV values than the lower laboratory normal limit, prior to treatment (Day 0) and posttreatment (Day 6 and Day 31, respectively; PCV ranging from 34.5 to 37.1%). Both of these dogs also had highly elevated BUN and creatinine at both time points suggesting an underlying chronic renal failure that could be the cause of the observed anemia. The third dog also had slightly lower PCV values than the lower laboratory normal limit the day before he died (see description below).

^{**}described in detail below. This table does not include a dog that died following surgery for splenic torsion (described below)".

In seven cases (6.5%), the adverse events were severe enough to warrant discontinuation of therapy. One of these seven cases was removed from the study by the owner after the dog vomited on Day 0. In 5 of these 7 cases, discontinuation of therapy resulted in resolution of the adverse event. In 2 cases, death ensued after termination of therapy. These cases are described in detail below:

- The first case was an 8.5 year old spayed German Shepherd weighing 38 kg. She vomited after the first dose was administered on Day 0. Vomiting was noted on subsequent days. By Day 4, the vomiting was described as repetitive and the investigator decided to terminate treatment and initiated symptomatic treatment (GI protectants and an antiemetic). Three days after termination of therapy, the dog presented with continuous vomiting and a diagnosis of splenic torsion was made. A splenectomy was performed that day at 7:30 pm. The dog recovered from anesthesia at 9:30 pm. Death occurred the following morning at approximately 5:00 am. Necropsy revealed an acute peritonitis caused by perforation of the duodenum. All other organs appeared normal. While the cause of death was definitively due to a splenic torsion, the investigator was unsure whether the splenic torsion initiated the dog's vomiting, or the vomiting initiated the splenic torsion.
- The second case was a 12 year old male German Shepherd weighing 38 kg. He received tepoxalin from Day 0 to Day 12. Diarrhea was reported from Day 3 to Day 12, vomiting on Day 8 and Day 11, and loss of appetite on Day 9. On Day 13, at the planned interim visit, the dog was scored as Greatly Improved by both the owner and investigator. Despite the clinical improvement, the investigator and owner decided to remove the dog from the study due to the diarrhea which was described as becoming darker. At the time of this interim assessment, the dog had a PCV of 35.5%, which was lower that its day 0 PCV of 52.3%. Despite evidence of GI bleeding, the dog was given 4 mg of dexamethasone IM. A spasmolytic agent (benzadamide) was also administered IM. The dog died the following night. No necropsy results were available for this dog.

This dog's initial bloodwork showed a white blood cell count (16.4 WBC/nL) with band neutrophils (2%). The dog had elevated liver enzymes (ALT = 122 U/L; SAP = 643 U/L). On day 13, the leukogram had worsened (WBC = 27.7/nL; band neutrophils = 11%).

Note: Lack of adherence to standard precautionary NSAID warnings contributed to the deaths of the two dogs in this study, including preexisting clinical abnormalities, inappropriate continuation of the use of tepoxalin in the face of GI abnormalities and concurrent use of corticosteroids.

Conclusions: The most commonly reported adverse reactions were related to GI abnormalities (diarrhea, vomiting, inappetance, soft feces, enteritis, death).

4. **HUMAN SAFETY:**

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure."

5. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that ZUBRINTM Tablets (tepoxalin), when used under labeled conditions of use in dogs, is safe and effective.

ZUBRINTM Tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

PATENT INFORMATION:

U. S. Patent No. 5,164,381 - Expires: November 17, 2009

U. S. Patent No. 4,826,868 - Expires: May 29, 2006

6. APPROVED LABELING:

- A. Package Insert
- B. Blister Foil
- C. Box Label
- D. Client Information Sheet

Package latert NADA 6141-183, Appressed by FDA

ZUBRIN" Rapidly-Disintegrating Tablets (tepoxalin)

NON-STEROIDAL ÁNTI-INFLAMMATORY DRUG

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For inchrist institution or to report suspected adverse reactions, call 1-600-224-5318.

PRECAUTIONS

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Table 3. Adverse Reactions Observed in Dogs That Participated in a Field Safety Study Treated With ZUBRIN Tablets for 26 Days

Adverse Reaction	Number of Dogs" (n = 107)	Modesa Number of Days Usserved (Range)
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Anoresta/Inappetance		\$ (1-15)
Enterals	7	3 (1-5)
Lethargy	•	3 (2-15)
Flatulence	1	31
Trembilno		27
Increased appetite	1	2
Esting orass	1	
Incontinence		•
Hair loss	1	es.
Death	l	

*Dogs may have accelerated more than one of the observations during the study.
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Made in the United Kingdom for Schering-Plough Animal Health Corp., Union, NJ 07083 USA

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Appended, DC, Ritchie, DM, et al. A Dual Cyclocopygensse/S-Upoxygensse Inhibitor of Anchi Metabolism With Present Aminimum and Achivity and A Favorible Gastrointestingl Profile. J. Exp. Ther. December 1994;271(3):1359-1408.

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United States Patent [19] Patent Number: 4,826,868 May 2, 1989 Wachter et al. Date of Patent: [54] 1,5-DIARYL-3-SUBSTITUTED PYRAZOLES [58] Field of Search 548/377, 378; 514/406, PHARMACEUTICAL COMPOSITIONS AND 514/407; 424/45 USE [56] References Cited [75] Inventors: Michael P. Wachter, Bloomsbury; U.S. PATENT DOCUMENTS Michael P. Ferro, Somerville, both of N.J. 3,974,176 8/1976 Rainer 548/377 4,095,025 6/1978 Newberry 548/378 Ortho Pharmaceutical Corporation, [73] Assignee: Raritan, N.J. Primary Examiner-Robert W. Ramsuer Attorney, Agent, or Firm-Benjamin F. Lambert [21] Appl. No.: 42,661 [22] Filed: Apr. 29, 1987 **ABSTRACT** 1,5-Diaryl-3-substituted pyrazoles, a method of their Related U.S. Application Data preparation, compositions containing the same and Continuation-in-part of Ser. No. 867,996, May 29, [63] methods of their use are disclosed. The pyrazoles are useful in alleviating inflammatory and cardiovascular disorders in mammals. [51] Int. Cl.⁴ A61K 31/415; C07D 231/12 [52] U.S. Cl. 514/407; 424/45; 548/378 14 Claims, No Drawings

1,5-DIARYL-3-SUBSTITUTED PYRAZOLES PHARMACEUTICAL COMPOSITIONS AND USE

This is a continuation-in-part of application Ser. No. 5 867,996, filed May 29, 1986.

DESCRIPTION

1. Technical Field

The present invention relates to substituted pyrazole 10 derivatives, and particularly to 1,5-diaryl 3-substitutedpyrazoles that are pharmacologically active in alleviating inflammation, asthma, hypersensitivity, myocardial ischemia, dermatological conditions such as psoriasis, such as inflammatory bowel syndromes, and to a method for synthesizing those pyrazole derivatives.

2. Background

Nonsteroidal anti-inflammatory drugs (NSAID's) fenoprofen and the like have generally been shown to attenuate the biosynthesis of prostaglandins by inhibiting the activity of the enzyme cyclooxygenase. The prostaglandin end-products of the cyclooxygenase pathway are responsible for many of the early signs of 25 inflammation including hyperalgesia, increases in vascular permeability leading to edema, and pyrexia. The activity and potency of the NSAID's reducing these signs and symptoms is, for the most part, correlated with their ability to inhibit prostaglandin biosynthesis. 30

The other major pathway of arachidonic acid metabolism is the lipoxygenase pathway. Lipoxygenase products of arachidonate metabolism, the leukotrienes, hydroxyeicosatetraenoic acids (HETES) and hydroperoxyeicosatetraenoic acids (HEPTES), have been shown 35 or implicated to be involved in disease states including acute and chronic inflammation, arthritis, allergic and other hypersensitivity disorders, dermatological diseases such as psoriasis, acne, atopic dermatitis, contact sensitivity, eczema and others, cardiovascular disorders 40 secondary to myocardial ischemia or infarction, thromboembolism or vasculitis or platelet aggregation, and hyperalgesic disorders, gynecological disorders such as dysmenorrhea, ocular inflammation, sperm motility or function, and others.

Leukotriene B₄ (LTB₄), another product of the lipoxygenase pathway, as well as HETES and HPETES can mediate induction of other phlogistic substances such as thromboxanes and prostacyclin, is chemotactic to inflammatory cells, and is hyperalgesic. Many of these 50 mediators have been identified in skin, lungs, coronary circulation, eyes, gastrointestinal tract and other organs, and in the synovial fluid of rheumatoid arthritic patients. In chronic inflammatory conditions such as rheumatoid arthritis, it is believed to be the chronic 55 influx of leukocytes, probably mediated by LTB4, that is the eventual cause of joint erosion.

It is believed that inhibitors of the lipoxygenase pathway could lead to a relatively permanent effect on inflammatory disorders such as rheumatoid arthritis since 60 they could modulate the actual mechanisms of tissue and joint breakdown. Similarly, drugs that could inhibit prostaglandin synthesis via the cyclooxgenase pathway could modulate and reduce early manifestations of inflammation. Pharmacologically active compounds that 65 can inhibit both enzyme pathways at similar concentrations (dual inhibitors) provide a more complete relief for patients suffering from arthritis, hypersensitivity,

dermatological, cardiovascular, gastrointestinal, ocular, and gynecological disorders than present drugs that inhibit one pathway, but not the other as is the case for usually used NSAID's that are predominantly inhibitors of the cyclooxygenase (prostaglandin synthesis) path-

A number of 1,5-diaryl-3-substituted pyrazoles are reported in the literature. Some of those pyrazoles have been reported to have pharmacological activity.

For example Fulmer et al., J. Het. Chem., 17: 799-800 (1980) report the synthesis of 1,3,5-triaryl pyrazoles, as do Foote et al., J. Het. Chem., 7: 89-92 (1970), Beam et al., J. Het. Chem., 9: 183-185 (1972); Soliman et al., J. Pharm. Sci., 70: 606-610 (1981), and Barluenga et al., dermatitis and gastrointestinal inflammatory conditions 15 J.C.S. Chem. Comm., 891 (1979). Soliman et al., J. Pharm. Sci., 70: 602-605 (1981) also report synthesis of 3-methyl-1,5-diarylpyrazoles in which the 1-position aryl is a phenylsulfonylurea or thiourea. Of the above reports, only the two reports by Soliman et al. discuss such as indomethacin, naproxen, ibuprofen, tolectin, 20 any pharmacological activity for the pyrazoles prepared or for analogs of those pyrazoles, and those materials are reported to have hypoglycemic activity.

Virmani et al., Indian J. Chem., Sect. B, 17B: 472-477 (1979) report the synthesis of 3-omega-alkylaminoalkyl pyrazoles among other compounds. The 1,5-diaryl-3substituted pyrazoles reported contained a phenyl group at the 1-position, a 4-nitrophenyl at the 5-position, and a $(CH_2)_n$ -NHCH₃ group at the 3-position, where n is 3, 4 or 5 (3-5). This report stated that the compounds prepared were screened for a number of biological activities, with nine of the ninety-four numbered compounds synthesized having mild anti-inflammatory activity, two others having diuretic activity and two others having weak anti-cancer activity. The above-discussed 1,5-diaryl-3-substituted pyrazoles were not among the compounds reported to have any pharmacological activity.

Vereshchagin et al., Zh. Org. Khim., 7: 907-912 (1971) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles. The 3-substituents were reported to be alkoxy alkylene in which the alkoxy radical was methoxy or phenoxy and the alkylene was methylene or isopropylene, while the 1,5-diaryl radicals were unsubstituted phenyl.

Jahn and Wagner-Jauregg, Arzneim-Forsch. (Drug Res.), 24: 494-499 (1974) reported the synthesis and some pharmacological activities of 1,5-diaryl-3-substituted-4,5-dihydropyrazoles. The aryl group at the 1-position for each reported compound was phenyl, while the 5-aryl substituent was reported to be phenyl, 4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl, and 2-hydroxyphenyl. The before-mentioned pyrazoles were substituted at the 3-position by bonding to the 3-position of propionic acid or propiohydroxamic acid. These compounds were said to possess antirheumatic activity.

Shawali et al., J. Het. Chem., 13: 989-92 (1976): Shawali, J. Het. Chem., 14: 375-81 (1977); and Matsumoto et al., Bull. Chem. Soc. Japan, 47: 946-949 (1979) reported the synthesis of 1,5-diaryl-3-substituted pyrazoles, all of which also included a substituent other than hydrogen at the 4-position on the pyrazole ring. Exemplary 4-position subtituents were reported to include cyano, amino, carboethyoxy, and phenylcarbonyl. These reports included no mention of biological activity of the compounds reported.

A series of benzimidoylpyrazoles was reported by Shrof et al., J. Med. Chem., 24: 1521-1525 (1981). These

compounds were reported to possess activities of sulfonyl urea and biguanide hypogleemics.

Biere et al., Arch. Phar., 316: 608-616 (1983) reported the synthesis of 1,4-diaryl-pyrazole-3-acetic acid derivatives, some of which also contained a an aryl substituent 5 at the 5-position. The synthesized compounds were assayed for use as anti-inflammatory drugs in rats. The compounds assayed that also contained 5-position substituents were reported to be relatively inactive.

A further group of 1,5-diphenyl-4-substituted- 10 pyrazole-3-acetic acids was reported by El-Sayed and Ohta, Bull. Chem. Soc. Japan, 46: 1801-1803 (1973). Those compounds were utilized as intermediates in the synthesis of pyrazolo-[4,3-c]-pyridines. Another group of 1,5-diphenyl-4-substituted-pyrazoles, some of which 15 also include methyl, phenyl and carboxymethyl groups at the 3-position, was reported in Al-Saleh et al., J.C.S. Perkin I, 642-645 (1981). The reports of El-Sayed and Ohta and those of Al-Saleh et al. make no mention of the pharmacological properties of the pyrazole deriva- 20 tives reported. Another group of 1,5-diaryl-3,4-disubstituted pyrazoles and 4,5-dihydro-5-hydroxy pyrazoles was reported in Fusco and Croce, Gazz. Chim. Ital., 101: 703-272 (1971).

SUMMARY OF THE INVENTION

The present invention contemplates 1,5-diaryl-3-substituted pyrazoles, their use and a method of their synthesis. The compounds of the present invention are pharmacologically active in alleviating inflammation, and inhibit the cyclooxygenase enzyme pathway, the lipoxygenase enzyme pathway, or preferably both pathwavs.

In particular, the invention contemplates a substituted pyrazole compound having a structure that con- 35 forms to the formula

$$R_1$$
 R_2
 R_3
 $N-N$
 $R-X$

wherein

 R_1 , R_2 , R_3 and R_4 are the same or different and are individually selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, amino, acetamido, phenyl, halo, hydroxy, lower alkylsulfonyl, lower alkylthio, nitro, trifluoromethyl, ω -trifluoromethyl lower 55 alkoxy, amino, acetamido, carboxy, alkylhydroxamic acid, or where R1, R2 or R3, R4 taken together with the phenyl group to which they are attached, form a naphthyl or substituted naphthyl group;

that contains 2-16 carbon atoms:

Y is hydrogen, bromo, chloro or lower alkyl having 1-4 carbon atoms;

and X is selected from the group consisting of carboxy, carboloweralkoxy, hydroxy, acetoxy, al- 65 kanoyloxy, lower alkoxy, lower alkyl carbonyl, oximo, cyano, amino, C(O)-R₅ and -C(O)C(O)-R₅ wherein R₅ is selected from the group consisting of hydrogen,

alkyl, lower alkoxy, NR6R7 wherein R6 and R7 are the same or different and are selected from the group consisting of hydrogen, and lower alkyl, or R6 or R7 are selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, hydroxy, lower acyloxy, benzyloxy, 2-hydroxy lower alkyl, lower carboxy alkyl, phenyl, substituted phenyl, pyridyl, thiazolyl, dihydrothiazolyl, w-alkanoate, 5-tetrazolyl, -OCO(CH2)-"COR9 wherein R9 is —OH, —ONa, dialkylamino such as diethylamino and morpholino, and n is 2 or 3; -0C0R₁₀ wherein R₁₀ is -CH₂NR₁₁R₁₂ wherein R₁₁ and R₁₂ are alkyl, such as methyl, cycloalkyl such as cyclohexyl, or together are a heterocyclic ring such as N-methylpiperazino, —OCOR₁₀ wherein R₁₀ is -CH2Cl, -CH2O-loweralkyl or t-butyl, -CH-loweralkyl-CO₂-Q, wherein Q is lower alkyl or -H, acyl such as acetyl, propionyl or butyryl; -NR8OH wherein R₈ is hydrogen, -CO-loweralkyl, -CO-tbutyl, —COC7 H₁₅, —CO-phenyl, SO₂-lower alkyl, -COCO₂—lower alkyl, and —COCONHOH; -NHR₁₃ wherein R₁₃ is hydrogen, -CO-lower alkyl, —CO-t-butyl, —COC₇H₁₅, —CO-phenyl, —SO₂-lower alkyl, —COCO₂—lower alkyl, —COCONHOH, -COCO₂H, COCON(lower alkyl)OH, and PO(O-lower alkyl)2; -C(R14)=NNH-2-thiazolino, -CH- $(OH)R_{14}$ and $-C(O)R_{14}$ wherein R_{14} is hydrogen, lower alkyl, phenyl and t-butyl; -C(=NOH)NH2 and -C(=NH)N(OH)-lower alkyl and O-NR₈R₉ wherein R₈ and R₉ are the same or different and are selected from the group consisting of hydrogen, lower alkyl, phenyl and substituted phenyl; with provisos that:

(a) when Y is bromo or chloro, X is -COOH, -CH-₂OH or -C(O)-R₅ wheren R₅ is NR₆R₇ and R₆ is OH and R7 is lower alkyl;

(b) at least one of R₁ and R₂ is other than hydrogen where (i) R-X is (CH₂)₂CO₂H or (CH₂)₂C(O)NHOH and (ii) R₃ and R₄ are 4-methoxy, 3-methoxy-4-hydroxy, 2-hydroxy and hydrogen; and

(c) at least one of R₁ and R₂, or one of R₃ and R₄ is other than hydrogen where R-X together contains three saturated carbon atoms linked together by carboncarbon bonds; and pharmaceutically acceptable salts

In preferred practice, R2 and R4 are hydrogen, and R₁ and R₃ are selected from the group consisting of halo, trifluroromethyl, lower alkyl and lower alkoxy, especially methoxy. R preferably contains two carbon atoms. It is also preferred that the X be hydroxyloweralkoxy, carboxy, a hydroxamic acid or a N alkyl hydroxamic acid; i.e., that X be C(O)NR₆R₇ where R₆ is hydroxy and R7 is hydrogen or lower alkyl or a N-alkyl hydroxamic acid; i.e. that X is -C(O)NR₆R₇ wheren R₆ is hydroxy or —OC(O)CH₂Z where Z is dialkylamino or -CH2CO2H and R7 is hydrogen or lower alkyl.

The present invention also contemplates a pharmaceutical composition that comprises an anti-inflammatory amount of an above-described substituted pyrazole R is a straight, saturated or unsaturated hydrocarbon 60 compound dispersed in a pharmaceutically acceptable carrier. The dose may be administered by topical, p.o., parenteral or aerosol routes. In preferred practice, that substituted pyrazole compound is capable of inhibiting both the cyclooxygenase and the lipoxygenase pathways in the amount present in the composition, when the composition is introduced into a mammal.

> Further contemplated is a method for alleviating inflammation in a mammal exhibiting an inflammatory

condition. That method comprises administering to that mammal a pharmaceutical composition that includes as the active ingredient an effective amount of an abovedescribed substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier for topical, oral, 5 parenteral and aerosol administration.

A method for synthesizing a 1,5-diaryl-3-(omega-substituted lower alkyl)pyrazole is also contemplated. In accordance with this method, an aryl hydrazine or its acid addition salt is reacted with a 1-aryl-(omega-sub- 10 stituted)-alkyl-1,3-dione containing at least 4 carbons in the alkyl chain. A polar solvent is used that is substantially inert to the reaction conditions, as is the omegasubstituent of the alkyl 1,3-dione. The resulting 1,5-diaryl-3-(omega lower alkyl substituted) pyrazole is there- 15 after preferably recovered, although it can be utilized in the form of its synthesis (crude form), as for further syntheses. Particularly preferred alkyl-1,3-dione derivatives contain 6 carbons in the alkyl chain and contain a hydroxy group as the omega-substituent.

The present invention provides several benefits and

A particular benefit of the invention is that it provides pharmacologically active compounds that are useful in treating inflammatory conditions.

A particular advantage of the present invention is that its synthetic method provides relatively high yields of 1,5-diaryl-3-(omega-substituted lower alkyl) pyrazole compounds.

Another benefit of the present invention is that some 30 of its pharmacologically active compounds inhibit the cyclooxygenase enzyme pathway, thereby providing a further means for studying that biological process.

Another advantage of the present invention is that some of its pharmacologically active compounds inhibit 35 the lipoxygenase enzyme pathway, thereby providing a further means for studying that biological process.

Still further benefits and advantages of the present invention will be apparent to those skilled in the art

DETAILED DESCRIPTION OF THE **INVENTION**

1,5-Diaryl-3-substituted pyrazole compounds, pharmaceutical compositions containing a substituted pyr- 45 azole compound as an active ingredient, a method of treating a mammal exhibiting an inflammatory condition and a method of synthesizing the substituted pyrazole compound are contemplated herein.

In the above formula, R₁, R₂, R₃ and R₄ are substitu- 50 ents on phenyl rings that substitute for hydrogen atoms at positions 1 and 5 of the pyrazole ring. It is preferred that at least one of R₁ and R₂, and one of R₃ and R₄ be substituted at the 4-positions of their respective phenyl

In examining the above structural formula to which the useful pyrazole compounds conform, it is noted that the R₁, R₂, R₃ and R₄ radicals and the X group can be a "lower" alkyl, "lower" alkoxy and the like. Groups and radicals referred to as "lower" denote that they 60 possess 1 to about 6 carbon atoms. The same is true for "lower" groups and radicals that are sustituents of the "lower" groups and radicals enumerated.

To the extent that X substituents are defined as being the same as those of R₁, R₂, R₃ and R₄, those commonly 65 defined substituents are discussed immediately below. Additional X substituents that are not common to X and R₁, R₂, R₃ and R₄ are discussed thereafter.

Lower alkyl radicals include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, npentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, octyl and the like.

Lower alkoxy radicals are oxygen ethers formed from a before-described lower alkyl group. Exemplary radicals include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, and the like.

Lower alkylthio radicals of R1, R2, R3 and R4 are sulfide ethers and are thus analogous to the oxygen ethers described above.

Halo radicals preferably include chloro and bromo, as well as fluoro and iodo.

Lower alkylsulfonyl radicals contain a beforedescribed lower alkyl radical bonded to an SO2 moiety that is itself also bonded to a phenyl ring. Exemplary lower alkylsulfonyl radicals thus include methylsul-20 fonyl, ethylsulfonyl, 2-ethylbutylsulfonyl and the like.

An omega-trifluoromethyl lower alkoxy radical is a lower alkoxy radical as before described that additionally includes a trifluoromethyl group at a position farthest on the alkyl chain from the place of bonding to the phenyl ring. Exemplary of such radicals are the 2,2,2trifluoroethoxy.

Naphthyl and substituted naphthyl radicals can replace an aryl group herein at either the 1- or 2-positions to provide 1-naphthyl or 2-naphththyl substituents. respectfully. Substituents on the naphthyl radicals can be any of those described herein as being useful aryl substituents. Exemplary substituted 1- and 2-naphthyls include 6-methoxy-2-naphthyl and the like.

Lower alkyl carboxy radicals are the beforedescribed lower alkyl radicals that further include a carboxy group. Exemplary lower alkyl carboxy radicals include carboxymethyl, 2-carboxyhexyl and the like. Lower alkyl lower alkoxy carbonyl radicals are lower alkyl esters of lower alkyl carboxy radicals. Exemplary from the detailed description and Examples that follow. 40 lower alkyl lower alkoxy carbonyl radicals include 3-isopropoxycarbonylpropyl, 4-hexyloxycarbonylpentyl and the like.

> A lower alkyl carbonyl radical contains a carbonyl group, a total of up to six carbon atoms, and with the portion of R to which it is linked, forms a ketone at the R/X junction. Exemplary lower alkyl carbonyl radicals include acetyl, propionyl 2-methylpropionyl, pentoyl and the like, which can also be named methyl carbonyl, ethyl carbonyl, isopropylcarbonyl and butylcarbonyl, respectively.

> Radicals in which X is C(O)—R₅ wherein R₅ is lower alkoxy are carboxylic esters. These esters are preferably named by considering R-X to be a single substituent entity. Exemplary R5 lower alkoxy groups are as before described, although methoxy and ethoxy are preferred. When R5 is NR6R7 and ONR8R9, it is also useful to consider R-X as a substituent entity.

> Lower hydroxy alkyl radicals of R6 and R7 are preferably 2-hydroxyethyl and 2-hydroxypropyl. Additionally useful lower hydroxy alkyl radicals include 4hydroxybutyl and the like.

> Substituted phenyl radicals that can comprise NR₆R₇ are the same as the substituted aryl groups described before wherein R₁, R₂, R₃ and R₄ comprise the substitu-

Pyridyl radicals are derivatives of pyridine and can be bonded to the nitrogen atom of NR₆R₇ at the 2-, 3- or 4-positions relative to the pyridine nitrogen.

R is the structural formula above is a straight, saturated or unsaturated hydrocarbyl radical that contains 2 to about 16 carbon atoms. In particularly preferred practice, the R—X radical together contains three saturated carbon atoms linked together by carbon-carbon 5 bonds. In other preferred embodiments, R is unsaturated and contains 7-16 carbon atoms.

R is a hydrocarbon radical and therefore contains no elements other than carbon and hydrogen. Consequently, any element present in R—X that is not hydrogen or carbon is, by definition, part of the X radical.

Pharmaceutically acceptable, non-toxic acid addition salts of 1,5-diaryl-3-substituted-pyrazole compounds are useful herein, and can be formed by treatment of the pyrazole with an appropriate acid. Exemplary inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric and the like acids. Exemplary organic acids include methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic and the like acids. Conversely, the acid addition salt form can be converted to the free base form by treatment with alkali.

1,5-Diaryl-3-substituted pyrazole compounds can include a carboxylic acid and/or a hydroxamic acid, as already noted. Basic salts of those carboxylic and hydroxamic acids are also contemplated, and are formed by treatment of the acid with an appropriate, non-toxic, pharmaceutically acceptable alkaline reagent to form a carboxylate or hydroxamate cation salt. Exemplary non-toxic, pharmaceutically acceptable cation salts of such carboxylic and hydroxamic acids include sodium, potassium, zinc, aluminum, calcium and magnesium. These salts also readily form in aqueous solutions of the carboxylic and hydroxamic acids.

In preferred practice, R_2 and R_4 are hydrogen, and R_1 and R_3 are selected from the group consisting of halo and lower alkoxy, especially methoxy. The preferred R_1 and R_3 substituents are preferably at the 4-positions of their respective aryl (phenyl) rings.

It is preferred that R contain two carbon atoms and 40 that X be carboxy, hydroxymethyl, a hydroxamic acid (N-hydroxy amide) or a N-lower alkyl hydroxamic acid (N-hydroxy-N-lower alkyl amide).

Specific, particularly preferred 1,5-diaryl-3-substituted pyrazole compounds are named hereinbelow, 45 followed by a parenthesized, underlined numeral for ease of identification and correlation with the syntheses and anti-inflammation study described in detail hereinafter.

The preferred species of this invention include:

- 1. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide, (3)
- 2. 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole, (2)
- 3. 5-(4-trifluoromethylphenyl)-3-(3-hydroxypropyl)- 55 1-(4-methoxyphenyl)pyrazole, (56)
- 4. 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl)pyrazole, (35)
- 5. sodium 8-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-5(Z)-octenoate, (32)
- 6. sodium 3-[5-(4-chlorophenyl)-1-(4-methoxy-phenyl)-3-pyrazolyl]propanoate, (13)
- 7. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide, (57)
- 8. N-carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-65 methoxyphenyl)-3-pyrazolyl|propanamide, (66)
- 9. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide (81)

- 10. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide (82)
- 11. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamide (83)
- 12. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenylpropanamide (84)
- 13. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamine (96)
- 14. 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanal (11)
- 15. 5-(4-chlorophenyl)-3-(3-oximinopropyl)-1-(4-methoxyphenyl)pyrazole (26)
- 16. 3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)pyrazole (55)

A pharmaceutical composition that comprises an anti-inflammatory amount of a before-discussed 1,5-dia-ryl-3-substituted pyrazole compound dispersed in a pharmaceutically acceptable carrier is also contemplated herein. The composition comprises a unit dosage of the substituted pyrazole compound.

The substituted pyrazole compounds of this invention are capable of inhibiting the lipoxygenase enzyme pathway and/or the cyclooxygenase (prostaglandin synthetase) enzyme pathway. In preferred practice, the substituted pyrazole compound of the pharmaceutical composition is capable of inhibiting both the lipoxyenase and the cyclooxygenase enzyme pathways in the amount at which that substituted pyrazole compound is present in the pharmaceutical composition, when the composition is introduced as a unit dose into an appropriate mammal such as a laboratory rat.

The term "unit dosage" and its grammatical equivalent is used herein to refer to physically discrete units suitable as unitary dosages for human patients and other warm blooded animals, each unit containing a predetermined effective, pharmacologic amount of the active ingredient calculated to produce the desired pharmacological effect in association with the required physiologically tolerable carrier, e.g., a diluent or a vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active ingredient, and (b) the limitations inherent in the art of compounding such an active ingredient for therapeutic use in humans and other animals. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, and the like, segregated multiples of any of the foregoing, as well as liquid solutions and suspensions.

The active ingredient is referred to herein as being dispersed in the carrier. Thus, the dispersion formed can be a simple admixture, a non-settling dispersion as in the case of certain emulsions, or as an ultimate dispersion, a true solution.

The amount of active ingredient that is administered in vivo depends on the age and weight of the mammal treated, the particular medical condition to be treated, the frequency of administration, and the route of administration. The dose range can be about 0.01 to about 500 milligrams per kilogram of body weight, more preferably about 0.1 to about 50 milligrams per kilogram of body weight and most preferably about 0.1 to about 25 milligrams per kilogram of body weight. The human adult dose is in the range of about 10 to about 2000 milligrams daily, given as a single dose or in 3 or 4 divided doses. Veterinary dosages correspond to human dosages with the amounts administered being in propor-

tion to the weight of the animal as compared to adult humans

As is seen from the data discussed hereinafter, orally administered unit doses containing about 1 to about 50 milligrams of a 1,5-diaryl-3-substituted pyrazole per 5 kilogram of laboratory rat body weight (e.g., about 200 grams each) were useful in reducing inflammation. These results are contrary to those reported by Virmani et al., Indian J. Chem., Sect. B, 17: 472-477 (1979) who reported compounds that are structurally similar to 10 those described herein were not active as anti-inflamma-

Physiologically tolerable carriers are well known in the art. Exemplary of liquid carriers are aqueous solutions that contain no materials in addition to the substi- 15 tuted pyrazole compound, or contain a buffer such as sodium phosphate at physiological pH value, saline and the like.

Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of 20 such additional liquid phases are glycerin and vegetable oils such as cottonseed oil.

Exemplary solid carriers (diluents) include those materials usually used in the manufacture of pills or tablets, and include corn starch, lactose, dicalcium phosphate, 25 thickeners such as tragacanth and methylcellulose U.S.P., finely divided SiO2, polyvinylpyrrolidone, magnesium stearate and the like. Antioxidants such as methylparaben and propylparaben can be present in both solid and liquid compositions, as can sweeteners such a 30 cane or beet sugar, sodium saccharin, sodium cyclamate and the dipeptide methyl ester sweeteneer sold under the trademark NUTRASWEET (aspartame) by G. D. Searle Co.

A method for alleviating inflammation in a mammal 35 exhibiting an inflammatory condition is also contemplated. The method comprises administering to that mammal an effective amount of a pharmaceutical composition that includes a unit dose of an active ingredient pound dispersed in a pharmaceutically acceptable carrier. The pharmaceutical composition is preferably maintained within the mammal until the substituted pyrazole compound is cleared from the mammal's body by natural means such as excretion or metabolism.

The pharmaceutical composition can be administered orally, topically or by injection, by means well known in the art. In preferred practice, the composition is administered orally as a tablet, capsule or aqueous dispersion.

Inasmuch as a pharmaceutial composition can be administered 3 to 4 times daily (per 24 hour period), the method of alleviating inflammation can include administering the pharmaceutical composition a plurality of times into the treated mammal over a time period of 55 weeks, months and years. The pharmaceutical composition is administered a plurality of times to the mammal over a time period of thirty days, in preferred practice.

A method for synthesizing a 1,5-diaryl-(omega-substituted lower alkyl) pyrazole constitutes yet another 60 aspect of the present invention. Here, an aryl hydrazine or its acid addition salt is admixed in an inert polar solvent with a 1-aryl-(omega-substituted)-alkyl-1,3dione containing at least 4 carbons, and up to about 9 carbon atoms, in the alkyl chain to form a reaction 65 mixture. The aryl hydrazine and the 1,3-alkyldione are preferably reacted in substantially stoichiometric amounts.

The omega-substituent of the 1-aryl-omega-substituted-alkyl-1,3-dione is substantially inert to the reaction conditions utilized for the cyclization reaction; i.e., the substituent does not itself react with any of the reactants or solvent during the cyclization reaction. Exemplary of useful substituents are hydroxy and lower alkoxy as before described. Hydroxy is particulary preferred as the omega substituent.

The aryl hydrazine and aryl-alkyl-1,3-dione are reacted in an inert polar solvent medium. Exemplary of such solvents are methanol, ethanol, isopropanol, pyridine, triethylamine and mixtures of those solvents.

The reaction mixture so formed is maintained with agitation, as by stirring, for a predetermined period of time for the 1-aryl-hydrazine and the 1-aryl-(omegasubstituted)-alkyl-1,3-dione to react and form the desired 1,5-diaryl-3-(omega-substituted lower alkyl) pyrazole. The predetermined time period is typically about I to about 20 hours, depending upon the reactants, solvent and reaction temperature.

The cyclization reaction is normally carried out at ambient room temperature. The temperature typically rises somewhat during the cyclization, but is readily controlled. Temperatures above room temperature can also be utilized.

The resulting substituted pyrazole can be used as is in its crude form directly after the cyclization, as where a further reaction is to be carried out with it. Preferably however, the crude reaction product formed is recovered and purified as by crystallization or column chromatography prior to use in a further reaction or to alleviate inflammation.

Further reactions can be carried out on the omegathat is the before-described substituted pyrazole com- 40 substituent of the pyrazole-3-lower alkyl group inasmuch as that substituent is substantially inert to the reaction conditions for cyclization and formation of the pyrazole ring, but need not be inert to all reaction con-45 ditions.

An exemplary, generalized reaction sequence is shown below in Scheme 1 where a 1-(R3,R4-disubstituted phenyl)-6-hydroxy-hexan-1,3-dione and R₁,R₂disubstituted phenyl hydrazine hydrochloride are reactants (A) and (B), respectively, that react to form 1-(R₁,R₂-disubstituted phenyl)-5-(R₃,R₄-disubstituted phenyl)-3-(3-hydroxypropyl)-pyrazole, I, wherein R₁, R2, R3 and R4 are as previously defined. The parenthesized numerals beneath the structual formula of I refer to compounds of that structure that are exemplified hereinafter.

The reaction sequence shown thereafter in Scheme 2 relates to reactions carried out with specific compounds and in which R* is the 1-[5-(4-chlorophenyl)-1-(4methoxyphenyl)-3-pyrazolyl]methylene group shown hereinafter); R₁-R₇ are as before described; lower case letters adjacent to reaction arrows indicate reaction conditions discussed thereafter below; and underlined numerals indicate specific compounds whose syntheses are described in detail hereinafter.

Scheme I

$$R_3$$
 R_4
 (A)
 R_1
 R_1
 R_2
 (B)

ing 1,3-diarylpyrazoles formed as minor products of the reaction.

The pyrazoles of formula I are oxidized to either the acid (e.g., 12) with, for example, Jones Reagent or to 5 the aldehyde (e.g., 11) with, for example, pyridinium chlorochromate, as illustrated with compound 2; i.e., 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole. The olefinic acid 32 was obtained by treatment of aldehyde 11 with (4-carboxylbutyl)tri-10 phenylphosphorane.

The appropriate acid chlorides were synthesized by treatment of acids of general formula 12 or 32 with oxalyl chloride in tetrahydrofuran (THF). The acid chlorides were then added as THF solutions to a solution of the appropriate alkylhydroxylamine hydrochloride [R₆NHOH(HCl)] in THF/water/triethylamine (THF/H₂O/Et₃N) to afford the alkylhydroxamic acids such as compounds 3, 58 and 41. The corresponding O-acylated products (e.g., 53 and 57) that may also form in the reaction were separated by either recrystallization or chromatography.

Similarly, treatment of the acid chlorides above with amines of general formula R₆R₇NH gave amides such as 28, 65 and 38, where R₆ and R₇ are as before defined.

Scheme 2

$$R^{\bullet}CH_{2}CH_{2}OH \xrightarrow{a} R^{\bullet}CH_{2}C$$

$$H$$

$$\downarrow b$$

$$\downarrow c$$

$$R^{\bullet}CH_{2}CH = CH - (CH_{2})_{3}CO_{2}H$$

$$\downarrow d$$

$$\downarrow d$$

$$\downarrow d$$

a. pyridinium chlorochromate: b. Jones Reagent: c, lithium hexamethyldisilazide/BrPh₃P(CH₂)₄CO₂H; d. oxalyl chloride: c. R₆NHOH: f. R₆R₇NH.

Treatment of the appropriate aryl diketone A wherein R₃ and R₄ are defined as before with arylhydra- 65 above gave acid 66. Zine B wherein R₁ and R₂ are defined as before gives the 1,5-diarylpyrazoles I that are isolated by recrystallization or chromatography on silica from the correspond- 2, aldehyde 11 or ac

Oxidation of compound 65 with Jones Reagent as above gave acid 66.

The remaining compounds of this invention were synthesized by standard methods from pyrazole alcohol 2, aldehyde 11 or acid 12 as shown in Scheme 3, below.

The substituted pyrazole compounds with unsaturated side chains at the 3-position were prepared by reaction of aldehyde 11 with the appropriate Wittig reagent, as discussed specifically hereinafter and shown in Scheme 5, above. R₁-R₇, lower case letters and underlined numerals are as described for Schemes 1 and 2, before. R* in Scheme 3 is the 1-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl-ethylene group, as shown.

Scheme 3

R°CH₂OH
$$\xrightarrow{a_1}$$
 R°CH₂OAc 2 $\xrightarrow{a_2}$

R*CH2OCOCH2COCH3 -b R*CH2OMe

$$R^{\bullet}-CO_2H \xrightarrow{c} R^{\bullet}-CO_2$$

$$R^{\bullet}$$
—CHO \xrightarrow{d} R^{\bullet} —CH=NOH

$$R^{\bullet}CHO \xrightarrow{e} R^{\bullet}CH(OH)Me \xrightarrow{f} R^{\bullet}CMe \downarrow e \downarrow R^{\bullet}C(OH)Me_2$$

R°CHO
$$\stackrel{q}{\longrightarrow}$$
 R°-CH=CHR°
$$R^{\circ} = (CH_2)_{11}CH_3, Ph, 4-CO_2Me-Ph$$

a₁, acetic anhydride/pyridine, a₂, 2.2.6-trimethyl-1,3-dioxen-4-one; b, NaH, methyl iodide; c, CH_2N_3 ; d, NH_2OH ; e, methyl magnesium bromide; f, pyridinium chlorochromate; g, lauryltriphenyl phosphonium bromide $\{BrPh_3P(CH_2)_{11}CH_3\}$ benzyltriphenylphosphonium chloride $\{PhCH_2^*Ph_3Cl^*\}$; $\{-emethoxycarbonylphenyl$ triphenylphosphonium chloride $\{-eCO_2MePhCH_2P^*Ph_3Cl^*\}$.

BEST MODES FOR CARRYING OUT THE INVENTION

Melting points (mp) were determined on a Thomas-Hoover apparatus, and are uncorrected. The infrared (IR) spectra were recorded on a Beckman Instruments IR-8 spectrophotometer and are expressed in reciprocal 60 centimeters. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a Varian T-60A or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. Parenthesized, underlined hydro-

gens were assigned to the resonance positions immediately before the parentheses. EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph or a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

EXAMPLE 1

5-(4-Chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole (2)

4-Methoxyphenylhydrazine hydrochloride [35.0 15 grams (g), 0.20 moles] was added to CH3OH [50 milliters (ml)] containing pyridine (20 ml). An additional amount of CH3OH (25 ml) was added to the thick resulting slurry. 1-(4-Chlorophenyl)-6-hydroxyhexan-1,3dione (48.2 g, 0.20 moles), was added neat, followed by more CH3OH (25 ml). The slurry was stirred at roomtemperature for 1.5 hours, after which time the mixture was concentrated and taken up in CHCl₃ (300 ml). The CHCl₃ solution was washed with 1N HCl (300 ml), dried (Na₂SO₄), fitered, and concentrated. The oil was decolorized (Norit) in hot diethyl ether (Et₂O) (300 ml). The Et₂O solution was cooled, and crystallization from Et₂O (300 ml) afforded 2 (49.4 g). From the filtrate was obtained additional 2 (9.28 g), total yield 91%, mp 87.5°-88°. NMR (CDCl₃) 1.7-2.3 (m, 2H, $CH_2CH_2CH_2$), 2.55 (brs, 1H, OH), 2.80 (t, 2H, J=7 Hz, CH_2), 3.75 (t, 2H, J=6 Hz, CH_2O), 3.77 (s, 3H, OCH_3), 35 6.28 (s, 1H, C₄—H), 6.93 (ABq, 4H, J=12, 9, 4—O-Me-C₆H₄), 6.9-7.3 (m, 4H, 4-Cl-C₆H₄); IR (KBr) 3320, 2920, 1495; MS, m/e 342 (M+), 312, 298 (100%);

Anal. Calcd. for C₁₉H₁₉ClN₂O₂: C, 66.56, H, 5.59; N, 8.17. Found: C, 66.54; H, 5.76; N, 8.02.

The following general procedure was used for the preparation of 1,5-diaryl-3-(3-hydroxypropyl)pyrazoles of Tables 1 and 2 that follow.

The appropriate aryl hydrazine or hydrazine hydrochloride B [10 millimoles (Mm)] was dissolved in a solution of methanol (25 ml) containing pyridine (1 ml). The appropriately substituted 1-aryl-1,3-dione A (10 50 Mm) was admixed in a single portion. In a short time, the mixture warmed slightly, darkened, and became homogeneous. After stirring at ambient temperature for a time period of from 2 to 20 hours, the reaction mixture 55 was worked up as follows: the mixture was concentrated in vacuo and taken up in diethyl ether (250 ml); the ether solution was washed with aqueous 1N HCl (200 ml), decolorized, dried (Na2SO4), filtered through a pad of celite, and concentrated in vacuo. The crude material was either purified by column chromatography (silica gel 60, 70-230 mesh, about 250 g, and elution with ether) to give the desired 1,5-diarylpyrazoles (I) or recrystallized directly without chromatography. In some cases the isomeric 1,3-diaryl isomer was also isolated in varying minor amounts, and eluted before I from the column.

TABLE 1

						Mass
Compound		Melting		Analy	/sis +	spectrum
Number	R ₁ §	point	c.	H.	N	m/e (M+)
1	4-H	105.5-106.5*	x	x	x	312 (M+)
2	4-OMe [#]	87-88°	x	X	x	342 (M+)
4	4-CI	85~87°	X	x	x	346 (M+)
5	3-CF ₃	oil	x	X	X	380 (M+)
35	4-Br	oil	x	X	x	390 (M+)
36	4-SO ₂ CH ₃	95-97°	x	x	x	390 (M+)
37	4-CH ₃	92-94*	x	x	x	326 (M +)
42	3.4-diOMe	113-114*	X	x	x	372 (M+)
46	3-OMe	oil	x	x	X*	342 (M+)
47	4-SMe	82-84°	x	x	x	358 (M+)
48	4-NO ₂	foam	X	x	x**	357 (M+)
51	4-OC5H11	oil	x	x	x	398 (M+)
52	[6-MeO - naphth-2-yl]	foam	х	x	x	392 (M+)
60	2-CF ₃	oil	X	x	x	
61	4-OCH ₂ CF ₃	87-89°	x	x	X	410 (MT)
8	3,4-diCl	oil	x	x	x	380 (M+)
22	2-OCH ₃	78-82°	x	x	x	312 (M+)
62	4-F	81-82°	x	X	x	330 (M+)
69	4-NH ₂	210-213	X	x	x***	327 (M+)
70	4-CON(OH)Me	98-100				385 (M+)
71	4-iPr	oil	x	хх		354 (M+)

TABLE 2

Compound Name	R ₁ §	R ₃	Melting point	Mass spectrum m/e (M±)
9	н	Н	oil	278 (M+)
10	4-OMe#	H	oil	308 (M+)
18	2-OMe	H	oil	308 (M+)
21	4-C1	н	oil	312 (M+)
30	4-OMe	4-F	86-87.5*	326 (M =)
50	3.4-diOMe	Н	oil	338 (M T)
54	4-OMe	4-Ph##	foam**	384 (M+)
55	4-OMe	4-Me	94.5-96*	322 (MT)
56	4-OMe	4-CF ₃	73-75	376 (M+)

TABLE 2-continued

	Compound Name	R ₁ §	R ₃	Melting point	spectrum m/e (M [±])
•	68	4-OMe	3,4-diCl	56-58*	376 (M ⁺)

45

50

55

Compounds in which R₁, R₂, R₃ and R₄ are all other than hydrogen can be synthesized by the above procedure. For example, when the aryl hydrazine B is 3,4-65 dimethoxyphenylhydrazine and the 1-aryl-1,3-dione A is 3,4-dichloro-4,6-dioxohexanoic acid, 5-(3,4-dichlorophenyl)-1-(3,4-dimethoxyphenyl)-3-(3-hydroxypropyl)pyrazole is obtained.

^{4°} dihydrate
***dihydrochloride, monohydrate

^{**} i hydrate

^{**}I hydrate
*hemihydrate
*Me = CH₃ 8 Re = CH₃ 8 R₂ and R₄ = H except for compounds 42 and 8, where R₂ = OMe and Cl, respectively.
*Tanalysis within experimental error for C, H & N.

^{**. &}amp;. *See Table 1 notes.

*** Ph = phenyl $^{9}R_{2}$ and R_{4} = hydrogen except for compounds 50 and 68, where R_{2} = OMe and R_{4} 60 = Cl. respectively.

TABLE 2'

Compound			Melting	Analysis			Mass Spectrum	
Number	R ₁ , R ₂	R'	Point	C,	H,	N	m/e (M+)	
72	4-OEt	CO ₂ H	123-125°	х	x	x	370	
73	4-OH	CO ₂ H	239~241°	x	x	x	342	
74	3,4-diOMe	CO ₂ H	153-154°	x	X	x	386	
75	4-0E1	CO ₂ Et	oil	x	X	X*	398	
76	4-OEt	-CON(OH)Me	foam	x	x	x**	341	
77	3,4-diOH	CO ₂ H	179-180*	x	x	x4.	358	
78	3,4-diOMe	-CON(OH)Me	162-163*	x	x	x	415	
103	2-OMe	- со ₂ н	135-137*	х	x	x	356	
104	2-OMe	-CON(OH)Me	145-147°	x	x	x	385	

TABLE 2"

Compound Number	R3, R4	Melting Point	Mass Spectrum (m/e)	C,	Н,	N	
105	4-Me	145-147°	336 (M+)	х	х	x	
106	3-Me	109-110°	336 (M+)	X	X	X	
107	3,4-di-Me	141-142*	350 (M+)	X	X	X	
108	2,4,6-tri-Me	141-142*	364 (M+)	х	X	X	
109	2-Me	111-112*	336 (M+)	X	X	X	
110	4-Et	137-138*	350 (M+)	X	X	X	

EXAMPLE 2

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]propionic acid (12)

To a solution of the alcohol 2 [(0.92 g, 2.68 millimoles (mM)] in acetone (25 ml) was added a 2N $H_2Cr_2O_7$ (Jones Reagent) solution (3.02 ml, 6.04 mM) dropwise 55 over a 10 minute time period. After stirring for 1 hour the reaction solution was decanted from the chromium precipitates on the sides of the reaction vessel. The reaction solution was concentrated in vacuo and taken up into ethyl acetate (EtOAc) (100 ml), washed with 60 distilled H_2O until the washes were clear, dried (MgSO₄), filtered, and concentrated in vacuo. Crystallization from Et_2O : hexane afforded 12 (0.88 g, 92%) as an off-white crystalline solid, mp=126°-128° C.

NMR: (CDCl₃) 2.7-3.2 (m, 4H, —CH₂CH₂—), 3.80 65 (s, 3H, —OCH₃), 6.30 (s, 1H, C₄—H), $\overline{6}$.7-7.5 (m, 8H, aromatic), 7.5-8.5 (1H, —COOH); IR (KBr) 1700; MS, m/e 356 (M+), 312, 311 (100%).

Anal. Calcd. for C₁₉H₁₇ClN₂O₃: C, 63.95; H, 4.80; N, 7.85. Found: C, 63.82; H, 4.92; N, 7.72.

EXAMPLE 3

Sodium

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]propanoate monohydrate (13)

To the acid 12 (1.0169 g, 2.85 mM) was added a 1.00N NaOH solution (2.85 ml, 2.85 mM) and distilled H₂O (15 ml). The reaction mixture was stirred until it was homogeneous, and then lyophilized to afford 13 (1.08 g, 98%) as a white solid, with a mp greater than 300° C.

NMR (CD₃OD) 2.3-3.2 (m, 4H, —CH₂—CH₂—), 3.80 (s, 3H, —OCH₃), 6.47 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatic); IR (KBr) 3250, 1640.

Anal. Calcd. for C₁₉H₁₆ClN₂NaO₃.H₂O: C, 57.51; H, 4.57; N, 7.06. Found: C, 57.19; H, 4.33; N, 6.98.

EXAMPLE 4

45 3-[5-(4-Chlorophenyl)-1-phenyl-3-pyrazolyl]propionic acid (17)

Following the procedure for compound 12 but substituting compound 1 for 2 afforded 17 (0.86 g, 68%) as a white crystalline solid, $mp=138^{\circ}-139^{\circ}$ C.

NMR (CDCl₅) 2.6-3.2 (m, 4H, —CH₂—CH₂—), 6.30 (s, 1H, C₄—H); 6.4-7.5 (m, 10H, aromatic and —COOH). IR (KBr) 3460, 1740; MS, m/e 326 (M⁺), 282, 281 (100%).

Anal. Calcd. for C₁₀H₁₅ClN₂O₂: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.48; H, 4.72; N, 8.59.

EXAMPLE 5

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methylpropanamide (3)

To a solution of the acid 12 (0.99 g, 2.77 mM) in tetrahydrofuran (THF) (20 ml) at 0° C., was added one drop of dimethyl formamide (DMF) and oxalyl chloride (0.29 ml, 33 mM). After 0.5 hours the cooling bath was removed and stirring was continued for an additional 0.5 hours. The reaction mixture was concentrated in vacuo to remove any excess oxalyl chloride, and the acid chloride of 12, was taken up into THF (10 ml).

To a solution of methylhydroxylamine hydrochloride (0.35 g, 4.16 mM) and triethylamine (Et₃N) (1.55 ml, 11.10 mM) in THF, H₂O (10 ml: 5 ml) at 0° C., was added the THF solution of the acid chloride dropwise over a 5 minutes period. The cooling bath was removed, and the reaction mixture was stirred for 1 hour, diluted to 100 ml with EtOAc, washed with H₂O, dried (MgSO₄), filtered, and concentrated in vacuo. Chromatography (Baker silica gel, 45 g) of the residue with EtOAc as eluent, followed by crystallization from Et₂O afforded pure 3 (0.70 g, 65%), mp=113°-115° C. Further recrystallization from ethyl acetate afforded white crystalline solid, m.p. 125°-26° C.

NMR: (CDCl₃) 2.7-3.5 (m, 4H, —CH₂CH₂—), 3.18 (broad s, 3H, —N—CH₃), 3.83 (s, 3H, —OCH₃), 6.30 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatic), 10.67 (broad s, 1H, —N—OH); IR (KBr) 3160, 1640; MS, m/e 385 (M+), 339 (100%).

Anal. Calcd. for C₂₀H₂₀ClN₃O₃: C, 62.25; H, 5.22; N, ₂₀ 10.89. Found: C, 62.60; H, 5.18; N, 10.82.

TABLE 2"

Com- pound Number	R1, R2	R3, R4	Melting Point	Mass Spectrum (m/e)	c,	Н,	N
111	4-OMe	4-Me	119-121*	365 (M+)	X	x	x•
112	4-Cl	4-OMe	158-160°	385 (M+)	Х	х	x
113	4-OMe	4-OMe	104-105*	381 (M+)	X	х	х
114	4-OMe	4-H	foam	351 (M+)	X	Х	X*
115	4-OMe	3-Me	137-138°	365 (M+)	Х	х	х
116	4-OMe	3,4-di- Me	130-131*	379 (M+)	Х	х	x
117	4-OMe	2,4,6- tri-Me	133-134°	393 (M+)	X	X	X
118	4-OMe	2-Me	117-118°	365 (M+)	X	х	x
119	4-OMe	4-Et	72-74°	379 (M+)	Х	Х	x

1 hydrate

TABLE 2"-AP

Compound Number	R3, R4	Melting Point	Mass Spectrum (m/e)	c.	н	
120	4-Me	139-141*	234 (M+)	Х	X	
121	3-Me	92-94*	234 (M+)	X	X	
122	3.4-di-Me	98-100°	248 (M +)	X	X	
123	2-Me	139-140*	234 (M ⁺)	X	X	
124	4-Et	114-115*	248 (M+)	X	X	
125	4-Cl	137-139*	254 (M +)	X	X	
126	4-F		238 (MT)	X	X	
127	3.4-di-Cl	87-90°	288 (M T)	X	X	

 Compound Number
 R3, R4
 Melting Point
 Spectrum (m/e)
 C, H

 128
 H
 102-105*
 220 (M+)
 X
 X

The following general procedure was used for the preparation of the 1,5-diaryl-3-pyrazole propionic acids of Table 2".

A mixture of the appropriate 6-aryl-4,6-diketohex-anoic acid (0.1 Mole) from Table 2"-AP in methanol (750 ml) containing Et₃N (0.2 Mole) was treated with 4-methoxyphenylhydrazine hydrochloride (17.4 g, 0.1 Mole) at room temperature for 1 hour. If the reaction was incomplete at this point, it was refluxed until complete. The resulting darkened solution was evaporated in vacuo and taken up in Et₂O (700 ml); the ether solution was washed with aqueous 1N HCl (350 ml), brine, dried (Na₂SO₄), decolorized, evaporated in vacuo and recrystallized from Et₂O.

The compounds of Table 2" were synthesized directly from the appropriate 4,6-diketohexanoic acid as described below.

Synthesis of 6-Aryl-4,6-diketohexanoic acids

The compounds of Table 2"-AP were synthesized by the following general procedure. To a reaction vessel containing anhydrous THF (250 ml) and diisopropylamine (14 ml, 0.1 Mole) stirring under nitrogen at 0° C. was added by syringe, n-BuLi (1.6M, 62.5 ml, 0.1 Mole). The vessel was then cooled to -78° C. Alternatively, 40 lithium hexamethyldisilazide (0.1 Mole) may be employed as the base in place of lithium diisopropylamide.

The appropriately substituted acetophenone (0.1 Mole) in anhydrous THF (50 ml) was added and the resulting solution allowed to stir for 30 minutes at -78° and succinic anhydride (4.0 g, 0.04 mole) in THF (100 ml) was added via syringe. The solution was allowed to stir for 1 hour at -78° , warmed to room temperature for 1 hour and poured into 5% HCl (250 ml). The mixture was extracted with Et₂O (2×300 ml) and the combined ether extract was extracted with 10% NaOH (100 ml). The NaOH layer was separated and acidified with 4N HCl, and reextracted with Et₂O (2×300 ml). The combined ether layers were dried (Na₂SO₄), filtered and concentrated in vacuo. The resultant residues were recrystallized from the appropriate solvent to give the compounds of Table 2"-AP.

EXAMPLE 6

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-N-hydroxy-N-methylpropanamide sodium salt monohydrate(3a)

To hydroxamic acid 3 (0.6052 g, 1.57 mM) was added 1.00N NaOH solution (1.57 ml, 1.57 mM) and distilled 65 H₂O (3 ml). The reaction mixture was stirred for 10 minutes at which time it was homogeneous. Lyophilization afforded pure 3a (0.64 g, 97%) as a white hygroscopic solid, mp=100°-100° c. (decomposed).

NMR: (CD₃OD) 2.3-3.4 (m, 4H, —CH₂CH₂—), 2.92 (broad s, 3H, —NCH₃), 3.78 (s, 3H, — \overline{O} CH \overline{I}_3), 6.47 (s, 1H, C₄—H), 6.7-7.6 (m, 8H, aromatic); IR (KBr) 3420, 1600; MS, m/e 384 (M-Na).

Anal. Calcd. for C₂₀H₁₉ClN₃NaO₃.H₂O: C, 56.40; H, 5 4.97; N, 9.87. Found: C, 56.24; H, 4.53; N, 9.70.

EXAMPLE 7

0-[2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]ethyl-carbonyl]-N-methylhydroxylamine (53)

The procedure to synthesize compound 3 was repeated on a twenty-fold scale.

Chromatography of the crude reaction mixture (Merck Silica Gel 60; 230–400 mesh, 150 g) with CH₃OH:CHCl₃ (3:97) as eluent, separated 3 from a mixture with the less polar component (2.5 g, R₂=0.18).

Chromatography (Merck Silica Gel 60; 230–400 mesh, 75 g) of this mixture with Et₂O as eluent, and crystallization from Et₂O:hexane afforded 53 (0.81 g, 3.7%) as a white crystalline solid, mp=80°-81° C. (sharp).

NMR: (CDCl₃) 2.83 (d, 3H, J=7.5 Hz, —NHCH₃), 2.6-3.3 (m, 4H, —CH₂CH₂—), 3.83 (s, 3H, —OC $\overline{\text{H}}_3$), 6.33 (s, 1H, C₄—H), $\overline{6}$.7- $\overline{7}$.4 (m, 4H, aromatic), 7.55 (q, J=7.5 Hz, 1H, —NHCH₃); IR (KBr) 3200, 1740; MS (20 eV EI), m/e 356, 339 (100%), 311, 297.

Anal. Calcd. for C₂₀H₂₀ClN₃O₃: C, 62.25; H, 5.22; N, 10.89. Found: C, 62.31; H, 5.21; N, 10.88.

EXAMPLE 8

N-Carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxy-phenyl)-3-pyrazolyl]-propanamide (66)

Following the procedure of Example 5, but substituting glycine for methylhydroxylamine hydrochloride afforded 66 (1.98 g, 67.4%), as a white crystalline solid, melting point=185.5°-187.5° C.

NMR (DMSO-d₆) 2.4–2.7 (m, 2H, —CH₂CH₋₂CON—), 2.7–3.0 (m, 2H, —CH₂CH₋₂CON—), 3.78 (s, 40 3H, —OCH₃), 3.78 (d, J=5.5 Hz, 2H, —NHCH₂COOH), 6.53 (s, 1H, C₄—H), 6.7–7.6 (m, 8H, aromatic), 8.29 (broad t, J=5.5 Hz, 1H, CONH-CH₂COOH); IR (KBr) 3360, 1725, 1665; MS, m/e 413 (M+), 311 (100%).

Anal. Calcd. for C₂₁H₂₀ClN₃O₇: C, 60.94; H, 4.87; N, 10.15. Found: C, 60.64; H, 4.87; N, 10.01.

EXAMPLE 9

3-[5-(4-Chlorophenyl)-1-phenyl-3-pyrazolyl]-N-hydroxy-N-methyl propanamide (67)

Following the procedure described in Example 5 but substituting compound 17 for compound 12 afforded 67 (1.24 g, 78.0%) as a white crystalline solid, 55 mp=155°-156.5° C.

NMR (CDCl₃) δ 2.5-3.5 (m, 4H, —CH₂CH₂—), 3.20 (s, 3H, —N(CH₃)OH), 6.33 (s, 1H, C₄H), 7.0-7.7 (m, 9H, aromatic). 10.37 (broad s, 1H, —N(CH₃)OH); IR (KBr): 3120, 1650; MS, m/e 355 (M+), 309 (100%).

Anal. Calcd. for C₁₉H₁₈ClN₃O₂: C, 64.13; H, 5.10; N, 11.81. Found: C, 64.17; H, 5.45; N, 11.51.

EXAMPLE 10

3-[5-(4-Fluorophenyl)-1-(4-methyoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl propanamide (45)

Following the procedure described in Example 5, but substituting compound 30 for compound 12 afforded 45

(1.21 g, 83%) as an off-white crystalline solid, mp = 151° - 154° C.

NMR (CDCl₃) 2.7-3.5 (m, 4H, —CH₂CH₂—), 3.20 (broad s, 3H, —NCH₃), 3.83 (s, 3H, — \overline{O} CH₃), 6.30 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatic), 10.4-10.9 broad s, 1H, —NOH); IR (KBr): 3140, 1650; MS (20 eV EI), m/e 369 (M $^{+}$), 340, 323 (100%).

Anal. Calcd. for C₂₀H₂₀FN₃O₃: C, 65.03; H, 5.46; N, 11.38. Found: C, 64.87; H, 5.59; N, 11.05.

EXAMPLE 11

Following the procedure described in Example 5, the following compounds were synthesized.

5	Com- pound Num-			Melting		Апа	lysis	Mass Spectrum m/e
	ber	R ₃	R'	Point	C,	H,	N	(M+)
o	81	Cl	iPr	80-83*	x	x	x*	413
	82	Cl	$\overline{}$	74–76°	X	x	x	453
5	83	CI	Et	113-114*	x	x	₹x	399
)	84	Cl	~	113.5-114.5	x	x	x	447
	79	CF ₃	Me	foam	x	x	x ² •	419
0	* 1 C6H14 2* 1 H2O							

EXAMPLE 12

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-N-hydroxypropaanamide (29)

To a solution of the acid 12 (0.97 g, 2.72 mM) in THF (20 ml) at 0° C., was added one drop of DMF (catalyst) and oxalyl chloride (0.28 ml, 3.26 mM). After 0.5 hour the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to remove any excess oxalyl chloride, and the remaining crude acid chloride, of acid 12, was taken up in THF (10 ml).

To a solution of hydroxylamine hydrochloride (0.28 g, 4.08 mM) and Et₃N (1.52 ml, 10.8 mM) in THF: H₂O (10 ml: 5 ml) at 0° C., was added the crude acid chloride solution, dropwise over a 5 minutes period. The cooling bath was removed, and the reaction mixture was stirred for 1 hour, diluted to 100 ml volume with EtOAc, washed with H₂O, dried (MgSO₄), filtered, and concentrated in vacuo. Crystallization from Et₂O afforded 29 (0.88 g, 87%) as a white crystalline solid, mp=154°-156° C.

NMR (CDCl₃) 2.4–3.4 (m, 4H, —CH₂CH₂—), 3.80 (s, 3H, —OCH₃), 6.30 (s, 1H, C₄—H), 6.3–7.5 (m, 9H, aromatic and —NH—). IR (KBr): 3260, 1665; MS, m/e 371 (M+), 353, 33 $\overline{9}$, 311, 298 (100%).

Anal. Calcd. for C₁₉H₁₈ClN₃O₃: C, 61.37; H, 4.88; N, 11.30. Found: C, 61.36; H, 5.05; N, 10.97.

EXAMPLE 13

0-[2-[5-(4-Chlorophenyl)-1-

(4-methoxyphenyl)-3-pyrazolyl] ethylcarbonyl]-N-tert-butylhydroxylamine

(57); and

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxypropanamide (58)

To a solution of the acid 12 (0.99 g, 2.77 mM) in THF (30 ml) at 0° C., was added one drop of DMF and oxalyl chloride (0.29 ml, 3.33 mM). After stirring for 0.5 hour the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to a volume of 10 ml, and added dropwise to a solution of N-(tert-butyl)hydroxylamine (HCl) (0.52 g, 4.16 mM) and E₃N (1.56 ml, 11.1 mM) in THF:H₂O (12 ml:6 ml) at 0° C. The reaction mixture was stirred for 1 hour, diluted to 100 ml with EtOAc, washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. The residue was combined with that from a similar run on a 2.72 mM scale.

Chromatography (Merck Silica Gel 60; 230–400 ²⁵ mesh, 72 g) with Et₂O:hexane (4:1) as eluent afforded 57, crystallized from cold Et₂O:hexane (1.19 g, 51%) as a white crystalline solid, mp=73°-74.5° C. and 58 recrystallized from EtOAc:Et₂O (0.63 g, 27%) as a white crystalline solid, mp=137°-138° C.

Compound 57, NMR (CDCl₃) 1.10 (s, 9H, $-C(CH_3)_3$), 2.7-3.4 (m, 4H, $-CH_2CH_2-$), 3.80 (s, 3H, $-OC\overline{H_3}$), 6.32 (s, 1H, C_4-H), 6.7-7.5 (m, 8H, aromatic); IR (KBr) 3480, 1730; MS (20 eV EI), m/e 339 (100%), 311, 297.

Anal. Calcd. for C₂₃H₂₆ClN₃O₃: C, 64.55; H, 6.12; N, 9.82. Found: C, 64.41; H, 6.19; N, 9.71.

Compound 58, NMR (CDCl₃) 1.25 (s, 9H, $-C(CH_3)_3$), 2.7-3.4 (m, 4H, $-CH_2CH_2-$), 3.83 (s, 3H, $-OCH_3$), 6.33 (s, 1H, C_4- H), 6.7-7.5 (m, 8H, aromatic), 10.08 (s, 1H, -N-OH). IR (KBr) 3460, 3130, 1620, 1590; MS (20 eV EI), m/e 427 (M+), 339 (100%), 311, 297.

Anal. Calcd. for C₂₃H₂₀ClN₃O₃: C, 64.55; H, 6.12; N, 45 9.82. Found: C, 64.62; H, 6.38; N, 9.72.

EXAMPLE 14

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propanal (11)

To a suspension of pyridinium chlorochromate (10.02 g, 46.5 mM) in CH₂Cl₂ (500 ml) was added the alcohol 2, (5.09 g, 15.5 mM). After stirring overnight, the reaction mixture was concentrated in vacuo to a volume of about 200 ml, and diluted to 1 liter with Et₂O. This 55 solution was filtered through celite, and the filter cake was washed with Et₂O (2×200 ml). The filtrate and the washes were combined and concentrated in vacuo. Chromatography (120 g, Baker silica gel) of the residue with Et₂O:hexane (2:1) as eluent, and crystallization 60 from Et₂O afforded pure 11, (0.88 g, 17%) as a white crystalline solid, mp = 101° - 102° C.

NMR (CDCl₃) 2.8-3.2 (m, 4H, $-CH_2CH_2CHO$), 3.85 (s, 3H, $-OCH_3$), 6.32 (s, 1H, C_4-H), 6.7-7.4 (m, 8H, aromatic), 9.93 (t, J=1 Hz, 1H, -CHO); IR (KBr) 65 1715; MS, m/e 340 (M+), 312 (100%).

Anal. Calcd. for C₁₉H₁₇ClN₂O₂: C, 66.96; H, 5.03; N, 8.22 Found: C, 66.72; H, 5.12; N, 8.13.

EXAMPLE 15

Sodium 8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-5(Z)-

octenoate (32).

To a solution of hexamethyldisilazane (5.25 ml, 24.9 mM) in THF (125 ml) at $\pm 5^{\circ}$ C. was added 1.46M n-butyl lithium (n-BuLi) (16.3 ml, 23.8 mM). The cool-10 ing bath was removed after 15 minutes and (4-carboxybutyl)triphenylphosphonium bromide (5.17 g, 11.7 mM) was added. Stirring was continued for 45 minutes and the aldehyde 11 (3.61 g, 10.6 mM) was added. After stirring for 1 hour, the reaction solution was diluted to a 600 ml volume with EtOAc and extracted with H2O (2×200 ml). The extracts were combined, acidified with 3N HCl, and extracted with EtOAc (2×200 ml). The EtOAc extracts were combined, dried (Na₂SO₄), filtered and concentrated in vacuo. Chromatography of the remaining residue (Baker silica gel, 160 g) with Et₂O as eluent afforded the acid (3.39 g, 75%) as a clear yellow oil.

To the neat acid (0.57 g, 1.34 mM) was added a 1.00N NaOH solution (1.34 ml, 1.34 mM) and a small amount of water. After stirring overnight, the reaction solution was lyophilized to afford 32 (0.60 g, 95%) as a white solid.

Acid, NMR (CDCl₃) 1.4–3.1 (m, 10H, $-CH_2CH_2CH = CH(CH_2)_3COOH$), 3.80 (s, 3H, $-O\overline{C}H_3$), 5.2–5.7 (m, $2\overline{H}$, -CH = CH -), 6.33 (s, 1H, $C_4 - H$), 6.7–7.5 (m, 8H, aromatic); MS (20 eV EI), m/e 426 (M+2), 424 (M+), 365, 351, 337, 298 (100%).

Compound 32, NMR (CD₃OD) 1.4-3.1 (m, 10H, -CH₂CH₂CH=CH(CH₂)₃—), 3.80-(s, 3H, -OCH₃), 35 5.2-5.7 (m, 2H, -CH=CH—), 6.45 (s, 1H, C₄—H), 6.7-7.5 (m, 8H, aromatic); IR (KBr) 3440, 1565; MS, m/e 423 (M—Na).

Anal. Calcd. for C₂₄H₂₄ClN₂NaO₃(1.25H₂O): C, 61.40; H, 5.69; N, 5.97. Found: C, 61.60; H, 5.46; N, 5.51.

EXAMPLE 16

8-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-5(Z)-octenamide (41)

Following the procedure described in Example 5, but substituting the acid for 12 afforded 41 (0.94 g, 62%) as a clear colorless oil.

NMR (CDCl₃) 1.5-3.5 (m, 14H, $-(CH_2)_2$ -CH=CH- $(CH_2)_3$ CON(CH₃)OH, 3.80 (s, 3H, $-OCH_3$), 5.3-5.7 (m, -CH- \overline{CH} -, 2H), 6.30 (s, 1H, C₄- \overline{H}), 6.7-7.4 (m, 8H, aromatic); IR (neat): 3160, 1630; MS (20 eV EI), m/e 455 (M+2), 453 (M+), 407, 379, 365, 298 (100%).

Anal. Calcd. for C₂₅H₂₈ClN₃O₃: C, 66.14; H, 6.22; N, 9.26. Found: C, 65.78; H, 6.55; N, 8.93.

EXAMPLE 17

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-N,N-diethylpropanamide (28)

To a solution of the acid 12 (1.01 g, 2.83 mM) in THF (25 ml) at 0° C., was added one drop of DMF and oxalyl chloride (0.30 ml, 3.40 mM). After 0.5 hours the cooling bath was removed and stirring was continued for 0.5 hour. The reaction mixture was concentrated in vacuo to remove the excess oxalyl chloride, and the remaining acid chloride was diluted with THF (25 ml) and cooled to 0° C. To this solution diethylamine (1.17 ml, 11.32 mM) was added dropwise over a 5 minute period. After

stirring for 1 hour, the reaction mixture was diluted to 100 ml with Et2O, washed with H2O, dried (MgSO4), filtered and concentrated in vacuo. Crystallization from Et₂O afforded 28 (0.98 g, 84%) as a yellow crystalline solid, mp=111°14 112° C.

NMR (CDCl₃) 1.13, 1.17 (2t, J=7 Hz, 6H, $-N(CH_2CH_3)_2$), 2.5–3.8 (m, 8H, $-CH_2CH_2$ — and $-N(CH_2CH_3)_2$), 3.80 (s, 3H, $-OCH_3$), 6.30 (s, 1H, C4-H), 6.7-7.4 (m, 8H, aromatic); IR (KBr) 1630; MS (20 eV EI), m/e 411 (M+), 311 (100%).

Anal. Calcd. for C23H26ClN3O2: C, 67.06; H, 6.36; N, 10.20. Found: C, 67.14; H, 6.34; N, 9.95.

EXAMPLE 18

Compounds of Table 3

Following the procedure of Example 17, but substituting NH4OH, 4-aminophenol, O,N-dimethylhydroxylamine hydrochloride, 2-aminophenol, 2-aminothiophenol, 2-aminopyridine and ethanolamine for diethylamine gave the compounds of Table 3.

TABLE 3

Com- pound Num- ber	NR ₆ R ₇	Melting Point	Mass Spectrum m/e	C,H.N
31	-NH ₂	 145-146*	355(M+)	xxx
34		223-226*	447(M ⁺)	xxx

	Com- pound Num- ber	NR ₆ R ₇	Melting	Mass Spectrum	 .
15		TVICOR /	Point	m/e	C.H.N
	44	—N(CH ₃)ОСH ₃	136-137°	399(M+)	xxx
20	40	-ин-	176-177*	432(M+)	xxx
25	63	OH _	198-200*	448(M ⁺)	xxx
30	64	-NH-	157.5- 159*	468(M+)	xxx
35	65	-NH-SH -NHCH ₂ CH ₂ OH		300/1/4	VVV.
-	- 63	-NACA2CH2OH	115-118**	399(M+)	XXX*
	*i hydrat	e			

In addition, following the procedure of Example 17, the following were synthesized.

Compound Number	NR ₆ R ₇	Melting Point	Mass Spectrum m/e	C.H,N
85	N	227-228*	440(M±)	xxx•
86	H -N-OMe	187.5-189*	461(M+)	xxx•
87	H -NCH ₂ CO ₂ Et	104-105.5*	441(M ⁺)	xxx

-continued

Compound Number	NR ₆ R ₇	Melting Point	Mass Spectrum m/e	C.H,N
88	H I −NCH2CONHOH	160-162°	428(M+)	XXX*
89	H —NCH2CON(OH)Me	180-182*	442(M+)	xxx
90	N-N	235-237*	423(M+)	xxx•
100	 -HN-CH(CO₂Et)CH₂SH		487(M ⁺)	xxx••
101	-HN-CH(CO2Et)CH2SCH3	93-96*	501(M+)	xxx

^{*} Hydrate

EXAMPLE 19

Compounds of Table 4

Following the procedure of Example 17 but substituting the acid for 12 and allowing the resulting acid chloride to react with NH4OH and diethylamine, respectively gave the amides of Table 4.

TABLE 4

$$N-N$$
 $N-N$
 NR_6R_7

Compound Number	-NR6R7	Melting point	Mass spectrum m/e	C,H,N
38	-NH ₂	125-127*	423(M+)	xxx
39	-NEt2*	oil	479(M+)	XXX

*Et = ethyl.

EXAMPLE 20

3-(3-Acetoxypropyl)-5-(4-chlorophenyl)-1-phenylpyrazole (7)

Compound 1 (1.00 g, 3.20 mM), acetic anhydride (1.0 ml, 11 mM), pyridine (1.0 ml, 12 mM) and CH₂Cl₂ (30 ml) were admixed and the admixture so formed was stirred overnight at room temperature, poured into H₂O 65 (150 ml) and extracted with CH2Cl2 (25 ml). The extracts were dried (Na₂SO₄), filtered and concentrated to an oil (1.1 g). Chromatography (silica gel 60; 70-230

mesh, 150 g) and elution with Et₂O afforded 1.10 g (94%) of 7 as a colorless oil.

NMR (CDCl₃) 2.05 (s, 3H, CH₃CO), 1.8-2.4 (m, 2H, $-CH_2CH_2CH_2$), 2.8 (dist t, J=8 Hz, CH₂—), 4.2 (t, 2H, J=6, $CH_{\overline{2}}O$), 6.32 (s, 1H, C_4 —H), 7.1-7.5 (m, 9H, aro-

IR (neat) 2960, 1740, 1600; MS, m/e 354 (M+), 311, 45 281, 268 (100%).

Anal. Calcd. for C20H19ClN2O2: C, 67.69; H, 5.40; N, 7.89 Found: C, 67.78; H, 5.36; N, 8.07.

EXAMPLE 21

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl methyl ether (24)

To a suspension of NaH (0.135 g of 60% oil suspension, 3.37 mM) in THF (10 ml) at $+5^{\circ}$ C. was added a solution of 2 (1.05 g, 3.06 mM) in THF (20 ml). After stirring for 30 minutes, methyl iodide (MeI) (0.21 ml, 3.37 mM) was added and the reaction mixture was left to stir overnight. After quenching with CH3OH, the reaction mixture was concentrated in vacuo, the residue was taken up in EtOAc, washed with H2O, dried (Na2. 60 SO₄), filtered, and concentrated in vacuo. Chromatography (40 g, Baker silica gel) with Et2O as eluent afforded 24 (0.98 g, 90%) as a clear yellow oil.

NMR (CDCl₃) 1.8-2.4 (m, 2H, -CH₂CH₂C-H₂OCH₃), 2.6-3.0 (m, 2H, —CH₂CH₂CH₂OCH₃), 3.35 (s, 3H, $-CH_2OCH_3$), 3.48 (t, $\overline{J}=7$ Hz, 2H, $-CH_2C_3$ H₂OCH₃), 3.78 (s, 3H, aromatic —OCH₃), 6.28 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatic); IR (neat) 1250, 830; MS, m/e 357 (M+1, 100%), 323 298.

Anal. Calcd. for $C_{20}H_{21}ClN_2O_2$: C, 67.31; H, 5.93; N, 7.85. Found: C, 67.15; H, 6.07; N, 7.77.

EXAMPLE 22

5-(4-Chlorophenyl)-3-(3-hydroxybutyl)-1-(4-methoxyphenyl) pyrazole (20)

To a solution of methyl magnesium bromide (MeMgBr) (2.20 ml, 7.04 mM) in Et₂O (15 ml) at 0° C. was added a solution of the aldehyde 11 (1.60 g, 4.69 mM) in Et₂O (70 ml) dropwise over a 30 minute period. After stirring for 1 hour the reaction was quenched with a saturated, aqueous NH₄Cl solution. The reaction mixture was partitioned between EtOAc and H₂O. The EtOAc solution was dried (MgSO₄), filtered, and conscentrated in vacuo. Chromatography (65 g, Baker 40 gm silica gel) of the residue with Et₂O as eluent afforded 20 (1.33 g, 79%) as a clear light yellow oil.

NMR (CDCl₃) 1.25 (d, J=6 Hz, 3H, —CH(OH-)—CH₃) 1.6-2.2 (m, 2H, —CH₂—CH(OH)—), 2.2-2.8 20 (m, $1\overline{H}$, —OH), 2.83 (t, J=7 \overline{Hz} , 2H, CH₂), 3.78 (s, 3H, —OCH₃), 3. $\overline{7}$ -4.2 (m, 1H, —CH₂— \overline{CH} (OH)—CH₃), 6.27 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatic); IR (neat) 3380; MS, m/e 356 (M+), 341, 312, 311, 298 (100%).

Anal. Calcd. for C₂₀H₂₁ClN₂O₂: C, 67.31; H, 5.93; N, 25 7.85. Found: C, 67.38; H, 6.35; N, 7.61.

EXAMPLE 23

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(3-oxobutyl)pyrazole (23)

To a suspension of pyridinium chlorochromate (3.65 g, 16.93 mM) in CH₂Cl₂ (20 ml) was added the alcohol 20, (3.02 g, 8.46 mM) in CH₂Cl₂ (15 ml). After stirring for 4 hours, the reaction solution was decanted from the chromium precipitates that were washed with EtOAc (2×150 ml). The reaction solution and the washes were combined, filtered through florosil, and concentrated in vacuo. Chromatography (120 g, Baker 40 gm silica gel) with Et₂O:hexane (1:1 to 100% Et₂O) as eluent, followed by crystallization from Et₂O:hexane afforded 23, (2.09 g, 70%) as a white crystalline solid, mp=85°-86°

NMR (CDCl₃) 2.20 (s, 3H, $-CO-CH_3$), 2.7-3.2 (m, 4H, $-CH_2CH_2-$), 3.78 (s, 3H, $-OCH_3$), 6.25 (s, 1H, 45 C₄-H), $\overline{6}$, 7-7.4 (m, 8H, aromatic); IR $\overline{(KBr)}$ 1715; MS, m/e 355 (M+1), 321, 311.

Anal. Calcd. for C₂₀H₁₉ClN₂O₂: C, 67.70; H, 5.40; N, 7.90. Found: C, 67.41; H, 5.24; N, 7.90.

EXAMPLE 24

5-(4-Chloropheny)-3-(3-hydroxy-3-methylbutyl)-1-(4-methoxyphenyl) pyrazole (27)

To a solution of MeMgBr (1.32 ml of 3.2M, 4.23 mM) in THF (15 ml) at 0° C., was added a solution of the 55 ketone 23, (1.00 g, 2.82 mM) in THF (25 ml) dropwise over a 20 minute period. After stirring for 1 hour, the reaction mixture was quenched with a saturated NH₄Cl solution, diluted to a 100 ml volume with Et₂O, washed with H₂O, dried (Na₂SO₄), filtered, and concentrated in 60 vacuo. Chromatography of the residue (Baker silica gel, 45 g) with Et₂O as eluent, afforded 27, (0.68 g, 80% corrected for recovered starting material) as a colorless

NMR (CDCl₃) 1.30 (s, 6H, —C(CH₃)₂OH), 1.7-2.2 65 (m, 2H, CH₂C—OH), 2.2-2.7 (broad s, 1H, —OH), 2.7-3.1 (m, $\overline{2}$ H, CH₂), 3.78 (s, 3H, —OCH₃), 6.25 (s, $\overline{1}$ H, C₄—H), 6.6-7.4 (\overline{m} , 8H, aromatic); IR (neat) 3390, 1250;

MS (20 eV EI), m/e 370 (M+), 355, 312 (100%), 311, 298.

Anal. Calcd. for C₂₁H₂₃ClN₂O₂: C, 68.01; H, 6.25; N, 7.55. Found: C, 67.80; H, 6.30; N, 7.24.

EXAMPLE 25

5-(4-Chlorophenyl)-3-(3-oximinopropyl)-1-(4-methoxyphenyl) pyrazole (26)

To a solution of the aldehyde 11 (1.00 g, 2.93 mM) in EtOH (30 ml) was added hydroxylamine hydrochloride (0.31 g, 4.40 mM) and pyridine (0.47 g, 5.87 mM). After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo. The remaining residue was taken up in CH₂Cl₂, washed with H₂O, dried (Na₂SO₄), filtered, and concentrated in vacuo. Crystallization from Et₂O:hexane afforded 26, (0.67 g, 64%) as a white crystalline solid, mp = 134° - 135° C.

NMR (CDCl₃) 2.5-3.3 (m, 5H, $-CH_2CH_2-$ and =N-OH), 3.78 (s, 3H, $-OCH_3$), 6.30 (s, 1H, C_4-H), 6.5-7.4 (m, 9H, aromatic and $-CH_2-CH=N-OH$); IR (KBr) 3210; MS (20 eV EI), m/e 355 (M+), 338 (100%), 311, 297.

Anal. Calcd. for C₁₉H₁₈ClN₃O₂: C, 64.13; H, 5.10; N, 11.81. Found: C, 63.79; H, 4.93; N, 11.53.

EXAMPLE 26

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-[3(Z)-hexadecenyl] pyrazole (33)

To a solution of hexamethyldisilazane (0.70 ml, 3.34 mM) in THF (30 ml) at $+5^{\circ}$ C. was added 1.55M n-BuLi (1.97 ml, 3.05 mM). The cooling bath was removed and after 15 minutes tridecyltriphenyl phosphonium bromide (1.68 g, 3.20 mM) was added. After stirring for 0.5 hour, the aldehyde 11 (0.99 g, 2.90 mM) was added, the reaction mixture was stirred for an additional 30 minutes, and concentrated in vacuo. The residue was taken up in Et2O:hexane (1:1), filtered, and concentrated in vacuo to afford crude 33 (1.42 g). Chromatog-40 raphy (Baker silica gel, 55 g) with Et₂O:hexane (1:2) as eluent afforded 33, (0.95 g, 65%) as a clear colorless oil. 0.7-3.1 **NMR** (CDCl₃) (m, 29H, $CH_2CH_2CH=CH(CH_2)_{11}CH_3),$ 3.80 3H. $-O\overline{C}H_3$), 5.3-5.7 (m, $\overline{2}H$, $-\overline{C}H$ =CH-), 6.30 (s, 1H, C₄—H), 6.6–7.5 (m, 8H, aromatic); IR (neat) 2940, 2860; MS (20 eV EI), 508 (M+2), 506 (M+), 449, 351, 338,

Anal. Calcd. for C₃₂H₄₃ClN₂O: C, 75.78; H, 8.55; N, 5.52. Found: C, 75.54; H, 9.03; N, 5.44.

EXAMPLE 27

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-[4-phenyl-3(E)-butenyl] pyrazole (14); and

5-(4-chlorophenyl)-1-(4-methoxyphenyl)-

3-[4-phenyl-3-(E,Z)-butenyl] pyrazole (15)

To a suspension of pyridinium chlorochromate (6.29 g, 29.2 mM) in CH_2Cl_2 (40 ml) was added the alcohol, 2, (5.00 g, 14.6 mM) in CH_2Cl_2 (30 ml). After stirring for 4 hours, the reaction solution was decanted from the chromium residue on the sides of the reaction vessel. This residue was washed with EtOAc (2×200 ml), and the washes were combined with the reaction solution, filtered through florisil, and concentrated in vacuo. Crystallization from Et_2O afforded the crude aldehyde 11 (4.20 g, 84%) contaminated with the dimer ester 16.

To a solution of hexamethyldisilazine (1.07 ml, 5.06 mM) in dry THF (50 ml) at $\pm 10^{\circ}$ C. was added n-BuLi

(2.98 ml, 4.62 mM). The cooling bath was removed, and after 15 minutes benzyltriphenyl phosphonium chloride (1.88 g, 4.84 mM) was added. After 45 minutes the crude aldehyde 11 (1.50 g, 4.40 mM) in THF (10 ml) was added, the reaction mixture was stirred for an additional 30 minutes and concentrated in vacuo. The residue was taken up into Et₂O (150 ml), filtered, and concentrated in vacuo.

Chromatography of this residue (Baker silica gel, 85 g) with Et₂O:hexane (1:1 to 100% Et₂O) afforded the E loolefin 14, the E/Z olefins 15, and dimer ester 16. Compound 14 was crystallized from Et₂O:hexane. All products were combined with those of an equivalent run using the same procedure on a 2.93 mM scale of the aldehyde 11. This afforded the E olefin 14, (1.33 g, 44%) as a white crystalline solid, mp=93*-95* C., the mixed E/Z olefin 15, 7:3 Z:E (1.12 g, 37%) as a clear colorless oil; and dimer ester 16 (0.40 g, 8.0%).

Compound 14 NMR (CDCl₃) 2.4-3.2 (m, 4H, —CH₂CH₂—), 3.80 (s, 3H, OCH₃), 6.2-6.7 (m, 2H, 20 CH=CH), 6.30 (s, 1H, C₄—H), 6.7-7.6 (m, 13H, aromatic); IR (KBr) 1245; MS, m/e 414 (M+), 310, 297 (100%).

Anal. Calcd. for C₂₆H₂₃ClN₂O: C, 75.26; H, 5.59; N, 6.75. Found: C, 75.45; H, 5.77; N, 6.77.

Compound 15, NMR (CDCl₃) 2.5-3.2 (m, 4H, —CH₂CH₂—), 3.80 (s, 3H, OCH₃), 5.5-6.7 (m, 2H, —CH=\overline{CH}—), 6.30 (s, 1H, C₄—H), 6.7-7.6 (m, 13H, aromatic); IR (neat) 1250; MS, m/e 414 (M+), 311, 297 (100%).

Anal. Calcd. for C₂₆H₂₃ClN₂O: C, 75.26; H, 5.59; N, 6.75. Found: C, 74.86; H, 5.96; N, 6.61.

EXAMPLE 28

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propyl

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propionate (16)

To a solution of the carboxylic acid 12 (0.40 g, 1.12 mM) in THF (10 ml) at 0° C., was added one drop of 40 DMF and oxalyl chloride (0.12 ml, 1.35 mM). After stirring for 15 minutes the cooling bath was removed and stirring was continued for 1 hour. The reaction mixture was concentrated in vacuo (to remove the excess oxalyl chloride), taken up in THF (10 ml), and 45 cooled to 0° C. To this solution was added the alcohol 2 (0.38 ml, 1.12 mM) and Et₃N (0.47 ml, 3.36 mM). After 15 minutes the cooling bath was removed and stirring was continued for 1 hour. The reaction mixture was diluted to 50 ml with Et₂O, washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. Chromatography (Baker silica gel, 45 g) with Et₂O:hexane (9:1) as eluent, afforded 16 (59%) as a white semisolid

NMR (CDCl₃) 1.8-2.4 (m, 2H, —CH₂CH₂CH₂—), 55 2.5-3.3 (m, 6H, —CH₂—CH₂CH₂COCOC \overline{H}_2 CH₂—), 3.80 (s, 6H, 2—OCH₃), $\overline{4}$.25 (t, J=6.5 Hz, 2H, — \overline{C} H₂C-H₂OCO—), 6.27+ $\overline{6}$.33 (2s, 2H, 2×C₄—H), 6.7-7.5 (m, $\overline{1}$ 6H, aromatic); IR (KBr) 1730; MS (DCI), 681 (M+1), 325

Anal. Calcd. for C₃₈H₃₄Cl₂N₄O₄: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.60; H, 4.90; N, 7.83.

EXAMPLE 29

3-[4-(4-Carbomethoxyphenyl)-3-(E)-butenyl]-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole (25)

. To a solution of hexamethyldisilazane (1.08 ml, 5.13 mM) in THF (50 ml) at +50° C. was added n-BuLi

(3.02 ml of 1.55M, 4.68 mM). After 15 minutes (4-carbomethoxyphenyl)triphenyl phosphonium chloride (2.19 g, 4.91 mM) was added, and the cooling bath was removed. After 30 minutes the aldehyde 11 (1.52 g, 4.46 mM) in THF (10 ml) was added, and the reaction mixture was stirred for an additional 0.5 hour. Concentration in vacuo of the reaction mixture and chromatography (Baker silica gel, 80 g) with Et₂O:hexane (1:1 or 100% Et₂O) as eluent afforded 25. Recrystallization from Et₂O afforded pure 25 (1.10 g, 48%) as a white crystalline solid, mp=126°-128° C.

NMR (CDCl₃) 2.5-3.1 (m, 4H, —CH₂CH₂—), 3.80 (s, 3H, —OCH₃), 3.90 (s, 3H, —COOCH₃), $\overline{5}.8$ -6.7 (m, 2H, —CH= \overline{C} H—), 6.30 (s, 1H, C₄— \overline{H}), 6.7-8.2 (m, 12H, aromatic); IR (KBr) 1725; MS, m/e 472 (M+), 441, 297 (100%).

Anal. Calcd. for C₂₈H₂₅ClN₂O₃: C, 71.10; H, 5.33; N, 5.92. Found: C, 71.30; H, 5.22; N, 5.97.

EXAMPLE 30

Methyl

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] propionate (19)

To a solution of the acid 12 (0.98 g, 2.75 mM) in Et₂O (10 ml) and CH₂Cl₂ (15 ml) at 0° C., was added a CH₂N₂ solution in Et₂O (prepared from N-nitroso-N-methylurea, 40% KOH/Et₂O) until a persistent yellow color was observed in the reaction mixture. The reaction mixture was dried (MgSO₄), filtered and concentrated in vacuo. Crystallization from EtOAc:hexane afforded 19 (0.85 g, 83%) as a white crystalline solid, mp=117°-118° C.

NMR (CDCl₃) 2.5-3.4 (m, 4H, —CH₂CH₂—), 3.70 35 (s, 3H, —COOCH₃), 3.80 (s, 3H, —OCH
3), 6.28 (s, 1H, C₄—H), 6.7-7.4 (m, 8H, aromatics). IR (KBr) 1730; MS, m/e 370 (M+), 339, 311 (100%).

Anal. Calcd. for C₂₀H₁₉ClN₂O₃: C, 64.77; H, 5.16; N, 7.56. Found: C, 64.47; H, 5.15; N, 7.65.

EXAMPLE 31

3-(3-Acetoacetoxypropyl)-5-(4-chlorophenyl)-1-(4-methoxyphenyl) pyrazole (59)

5-(4-Chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole (1.71 g, 0.005 moles) and 2,2,6-trimethyl-1,3-dioxen-4-one (0.71 g, 0.005 moles) were disolved in 100 ml of xylenes. The solution was stirred under reflux for 16 hours. At that time, the solution was cooled to room temperature, and concentrated in vacuo to a yellow oil. The oil was flash chromatographed on silica gel to afford 59 (1.7 g, 80%) as a pale yellow oil.

NMR (CDCl₃) 1.8-2.4 (m, 2H, CH₂CH₂CH₂), 2.1 (s, 3H, COCH₃), 2.8 (t, 2H, J=7 Hz, CH₂), 3.48 (s, 2H, COCH₂CO), 3.85 (s, 3H, OCH₃), 4.25 (t, 2H, J=7 Hz, CH₂OCO), 6.25 (s, 1H, C₄— \overline{H}), 6.9 (d, J=8 Hz, 2 aromatic H), 7.0-7.4 (m, 6H, aromatic H); IR (neat) 1750, 1725; \overline{M} S, m/e 426 (M+), 341.

Anal. Calcd. for C₂₃H₂₃ClN₂O₄: C, 64.71; H, 5.43; N, 6.56. Found: C, 64.97; H, 5.67; N, 6.13.

EXAMPLE 32

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propylamine (96)

To a suspension of LiAlH₄ (0.13 g, 3.5 mM) in THF (15 mL) was added a solution of the amide 31, (1.00 g, 2.81 mM) in THF (15 ml), dropwise, keeping the reac-

tion temperature below reflux. The reaction mixture was heated to reflux, and refluxed for 17 hours, when it was quenched with 0.13 ml H₂O, 0.13 mL 20% NaOH solution and an additional 0.39 ml H₂O. The reaction mixture was filtered and concentrated in vacuo. The 5 remaining residue was taken up into EtOAc (50 mL) and extracted with a 1.0N HCl solution (2×25 mL). The aqueous extracts were combined and washed with EtOAc (25 mL), neutralized with a 2N NaOH solution, and extracted with EtOAc (2×50 mL). The organic 10 extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to afford the title compound (0.86 g, 90%) as a light yellow oil.

NMR (CDCl₃) 1.6–2.3 (m, 4H, —CH₂CH₂CH₂NH₂), 2.6–3.1 (m, 4H, —CH₂CH₂CH₂NH₂), $\overline{3}$.78 (s, $\overline{3}$ H, 15—OCH₃), 6.27 (s, 1H, C₄—H), 6.6–7.5 (m, 8H, aromatic); IR (neat) 3380, 1520; MS (DCI), m/e 344 (MH++2), 342 (MH+, 100%).

Anal. Calcd, for C₁₉H₁₆ClN₃0: 67.55; H, 4.77; N, 12.44. Found: C, 67.23; H, 4.88; N, 12.21.

EXAMPLE 34

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-methyl-N-succinyloxy-propanamide (12a)

To a solution of the hydroxamic acid 3 (5.0 g, 12.96 mM) in dry pyridine (13 ml) was added succinic anhydride (1.3 g, 12.99 mM) in pyridine (5 ml) and the resulting solution was stirred for 72 hours. The pyridine was removed in vacuo and the residue was triturated with hexane and recrystallized from Et₂O to afford pure 34 (6.21 g, 98%) as a white solid, mp=146°=147°. MS, m/e 485(M+).

Anal. Calcd. for C₂₄H₂₄ClN₃O₆: C, 59.32; H, 4.98; N, 8.65. Found: C, 59.68; H, 4.97; N, 8.75.

Employing a similar procedure, the compounds of Table 5 were synthesized.

TABLE 5

Compound Number	R3,R4	R'_	Melting Point	Mass Spectrum (m/e)	C,H,N
130	4-Me	CH ₂ CH ₂ CO ₂ H	131~132*	465(M+)	xxx
131	3,4-di-Me	CH2CH2CO2H	124-125*	479(M+)	XXX
132	4-C1	CH2CH2CH2CO2H	glass	385(M-114)	XXX
133*	4-Cl	CH ₂ CH ₂ CO ₂ Na	240°(dec)	507(M+)	XXX

^{*}Prepared as the sesquihydrate by treatment of compound prepared in Example 34 with 1N NaOH

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Anal. Calcd. for C₁₉H₂₀ClN₃O: C, 66.76; H, 5.90; N, 12.29. Found: C, 66.70; H, 5.97; N, 11.83.

EXAMPLE 33

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanenitrile (95)

To a suspension of compound 31, (7.75 g, 21.8 mM) in dry benzene (400 mL) was added SOCl₂ (4.78 mL, 65 55 mM). The reaction mixture was heated to reflux for three days and then cooled to 0° C. Any excess SOCl₂ was decomposed with ice water. 50 mL of H₂O was added to the reaction mixture which was then neutralized with 50% NaOH, washed with H₂O (2×50 mL), 60 dried (Na₂SO₄), filtered, and concentrated in vacuo. Crystallization from Et₂O, Hexane afforded the title compound (6.43 g, 87%) as a light yellow crystalline solid, mp=107°-109° C.

NMR (CDCl₃) 2.4=3.2 (m, 4H, $-CH_2CH_2-$), 3.82 65 (s, 3H, OCH₃), 6.41 (s, 1H, C₄-H), 6.7-7.5 (m, 8H, aromatic); IR (KBr) 2250, 1510; MS(EI) m/e 339 (M+2, 1Cl), 337 (M⁺, 100%).

EXAMPLE 35

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-N',N'-dimethylglycinyloxy-N-methylpropanamide (134)

Compound 3 (6.0 g, 15.55 mM) was added to a suspension of N,N-dimethyl-glycine (1.61 g, 15.61 mM) and N',N'-dicyclohexylcarbodiimide (3.21 g, 15.55 mM) in dry pyridine (22 ml) under nitrogen and stirred for 44 hours. The solvent was removed in vacuo and the residue triturated with CH_2Cl_2 , filtered, and the filtrate evaporated to dryness. Recrystallization from CH_2Cl_2/Et_2O afforded pure 35 (6.8 g, 93%) as a white solid, mp=103°-104°, MS, m/e 470 (M+).

Anal. Calcd. for C₂₄H₂₇ClN₄O₄: C, 61.20; H, 5.78; N, 11.90. Found: C, 61.26; H, 5.94; N, 11.79.

The oxalate salt of 35 was synthesized as the trihydrate as a white solid,

 $mp = 114^{\circ}-115^{\circ}$.

Anal. Calcd. for C₂₄H₂₇ClN₄O₄.C₂H₂O₄,3H₂O: C, 50.77; H, 5.74; N, 9.11. Found: C, 50.68; H, 5.73; N, 8.64. In a similar manner, the compounds of Table 6 were synthesized.

TABLE 6

				Mass		
Compound Number	R3,R4	R'	Melting Point	Spectrum (m/e)	C,H,N	
135	4-C1	c-C ₅ H ₉ NHCO ₂ t-Bu	155-156*	596(M+)	XXX	
136	4-Cl	CH2CH2COMorpholine	108-109*	554(M+)	XXX	
137	4-Ci	CH2CH2CONE12	43-44*	540(M+)	XXX*	
138	4-Me	CH ₂ NMe ₂	77-78°	450(M+)	XXX	

[°]i hydrate

EXAMPLE 36

3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl] N-Chloroacetyloxy-N-methylpropanamide (139)

To a solution of 3 (7.0 g, 18.14 mM) in anhydrous 35 THF (125 ml) was added methylmorpholine (1.99 ml, 18.1 mM) and the resulting solution was cooled to -10° C. under nitrogen. Chloroacetyl chloride (1.44 ml, 18.1 mM) was added and stirred for 10 minutes, filtered and the filtrate concentrated in vacuo. The residue was recrystallized from Et₂O to afford pure 36 (5.7 g, 68%) as a white solid, $mp = 110^{\circ}-111^{\circ}$. MS, m/e 461 (M+).

Anal. Calcd. for C22H21Cl2N3O4: C, 57.15; H, 4.58; N, 9.09. Found: C, 57.42; H, 4.55; N, 8.99.

Employing a similar procedure to that of Example 36, 45 the compounds of Table 7 were synthesized.

TABLE 7

Compound Number	R'	Melting Point	Mass Spectrum (m/e)	C,H,N
140	CHi	130-132*	427(M+)	XXX
141	C(CH ₁) ₃	144-145*	469(M+)	XXX
142	CH ₂ OMe	98-100	457(M+)	xxx•

"} hydrate

Following the procedure of Example 5, but using the appropriate hydroxylamine gave the compounds of Table 8.

TABLE 8 30

Compound Number	R'	Melting Point	Mass Spectrum (m/e)	C,H,N
143	CH2CH2Pyr	glass	695(M+)	XXX*
144	CHMeCO2Et	125-127*	471(M+)	XXX
145	CHMeCO ₂ H	148-150°	443(M+)	XXX
146	C8H17	oil.	483(M+)	XXX

" hydrate

EXAMPLE 37

i

3-[4-Bromo-5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propionic acid (147)

The acid 12 (3.57 g, 10 mM) and N-bromosuccini-50 mide (1.78 g, 10 mM) were dissolved in a mixture of CCl₄ (150 ml) and CHCl₃ (20 ml) and allowed to stir for 16 hours. The solvents were evaporated in vacuo and the residue was dissolved in CHCl3, washed with H2O, dried (Na₂SO₄), filtered and evaporated to give an oil 55 which was crystallized from Et₂O to afford pure 37 (2.18 g, 50%) as a white solid, mp= $147.5^{\circ}-148^{\circ}$. MS, m/e 435 (MH+).

Anal. Calcd. for C₁₉H₁₆BrClN₂O₃: C, 52.37; H, 3.70; N, 6.43. Found: C, 52.58; H, 3.69; N, 6.27.

Substitution of N-chlorosuccinimide for Nbromosuccinimide gave the corresponding 4-chloro derivative as a white solid, mp=123.5°-124.5°. MS, m/e 391(MH+). (compound No. 182)

Anal. Calcd. for C₁₉H₁₆Cl₂N₂O₃,1/4H₂O: C, 57.66; 65 H, 4.20; N, 7.08. Found: C, 57.78; H, 4.12; N, 6.96.

Using the acids synthesized in Example 37 and following the procedure described in Example 5 gave the compounds of Table 9.

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TABLE 9

Compound				Melting	Mass Spectrum	
Number	x	R3,R4	R	Point	(m/e)	C,H,N
148	Br	4-Cl	Me	foam	463(M+)	XXX
149	Cl	4-C1	Me	foam	419(M+)	XXX*
150	Br	4-CI	Н	150-151*	449(M+)	XXX

•hydrate

Substituting Compound 2 for the acid 12 in Example 37 afforded 4-bromo-5-(4-chlorophenyl)-3-(3-hydroxy-propyl)-1-(4-methoxyphenyl)pyrazole, as an off-white solid, 87%, mp=118.5°-120°. (compound No. 183) MS, m/e 420 (M+).

Anal. Calcd. fo C₁₉H₁₈BrClN₂O₂: C, 54.11; H, 4.30; N. 6.64. Found: C, 54.20; H, 4.35; N. 6.59.

Following a similar procedure, but employing N-chlorocuccinimide gave 4-chloro-5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole as a ³⁰ tan solid;

 $mp = 113^{\circ}-115^{\circ}$. MS, m/e 376 (M+) (Compound No. 184).

Anal. Cald. for C₁₉H₁₈Cl₂N₂O₂: C, 60.49; H, 81; N, 7.43. Found: C, 60.30; H, 4.82; N, 7.36.

EXAMPLE 38

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]hydroxyl-amine (151)

To a solution of the oxime 26 (2.70 g, 7.59 mM) in MeOH (50 ml), containing methyl orange (2 mg) as as indicator, was added a solution of NaBH₃CN (0.52 g, 8.4 mM) in MeOH (20 ml), and a solution of 2N HCl, simultaneously, at such a rate to maintain a pH of 3 to 4. The reaction was stirred for 3 hours at room temperature, acidified to pH 1 and concentrated in vacuo. The residue was diluted with H₂O (100 ml), adjusted to pH 8.5 with 5N NaOH, and extracted with EtOAc. The extracts were combined, dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was chromatographed on Merck Silica Gel 60 (90 g, 230–400 mesh) with EtOAc:MeOH (9:1) as eluent. Crystallization from Et₂O afforded pure 38 (1.64 g, 60%) as a white solid, mp=91°-93°. MS, m/e 357(M+).

Anal. Calcd. for C₁₉H₂₀ClN₃O₂: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.63; H, 5.74; N, 11.63.

EXAMPLE 39

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-propyl]-N-hydroxy-acetamide (152)

To a solution of hydroxylamine 38 (1.25 g, 3.49 mM) and Et₃N (0.97 ml, 6.9 mM) in THF (35 ml) was added acetyl chloride (0.25 ml, 3.5 mM) and the reaction mixture stirred for 1 hour, diluted with EtOAc (165 ml), 65 washed with H₂O, dried (Na₂SO₄), filtered and concentrated in vacuo to give a residue which was recrystallized from EtOAc:Et₂O to afford pure 39 (1.06 g, 76%)

as a white crystalline solid, $mp = 121^{\circ}-123^{\circ}$. MS, m/e 399 (M+).

Anal. Calcd. for C₂₁H₂₂ClN₃O₃: C, 63.07; H, 5.55; N, 10.51. Found: C, 62.83; H, 5.95; N, 10.43.

Following a similar procedure to that of Example 39 and employing the appropriate acyl chloride afforded the compounds of Table 10.

TABLE 10

Compound Number	R.	Melting Point	Mass Spectrum (m/e)	C,H.N
153	CO-t-Bu	138-140°	441(M+)	XXX
154	COC7H15	90-91*	483(M+)	XXX
155	COPh	foam	461(M+)	XXX
156	SO ₂ CH ₃	173-175°	435(M+)	XXX

EXAMPLE 40

Ethyl

N-[3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]-hydroxyoxamate (157)

Following a similar procedure to that of Example 39, but employing ethyl oxalyl chloride in place of acetyl chloride afforded 40 as a white foam; MS, m/e 457 (M+).

Anal. Calcd. for C₂₃H₂₄ClN₃O₃: C, 60.33; H, 5.28; N, 9.18. Found: C, 60.55; H, 5.67; N, 9.18.

EXAMPLE 41

N-[3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propyl]-N,N'-dihydroxyoxamide (158)

To a solution of hydroxylamine.HCl (0.25 g, 3.5 mM) and the ester 7C (0.81 g, 1.8 mM) in EtOH (17 ml) was added a 1N NaOEt solution (7.1 ml, 7.1 mM). After stirring for 2.5 hours the reaction mixture was acidified and concentrated in vacuo. The residue was diluted with CHCl₃, washed (H₂O), dried (Na₂SO₄), filtered and concentrated in vacuo. Crystallization from EtOAc:Et₂O afforded pure 41 as a white crystalline solid, mp=145°-146.5° MS, m/e 444 (M+).

Anal. Calcd. for $C_{21}H_{21}ClN_4O_5.0.25$ H_2O : C, 56.13; H, 4.82; N, 12.47. Found: C, 56.16; H, 4.76; N, 12.32.

EXAMPLE 42

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-ethylamine 159

To a solution of the acid 12 (1.0 g, 2.8 mM) in benzene (25 ml) was added Et₃N (0.39 ml, 2.8 mM) and di60 phenylphosphoryl azide (0.60 ml, 2.8 mM). After stirring overnight at room temperature, the reaction mixture was heated to 70° C. for 1.5 hours, cooled and
concentrated in vacuo. Dioxane (2 ml), followed by a
solution of concentrated HCl (0.3 ml) in dioxane (2 ml)
65 was added, and the reaction mixture was heated to
reflux for 2 hours, cooled and diluted to 50 ml with
EtOAc. The organic solution was washed with a 0.25N
NaOH solution, and extracted with 1N HCl. The ex-

tracts were combined, basified with 5N NaOH, and extracted with EtOAc, dried, filtered and concentrated in vacuo. Crystallization from Et₂O afforded pure 42 (0.62 g, 68%) as a light yellow crystalline solid, mp=95°-97°. MS, m/e 327 (M+).

Anal. Calcd. for C₁₈H₁₈ClN₃O: C, 65.95; H, 5.53; N, 12.82. Found: C, 66.14; H, 5.57; N, 13.10.

EXAMPLE 43

Ethyl

2-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-ethylamine-N-oxoacetate 160

To a solution of the amine 42 (3.24 g, 9.8 mM) and Et₃N (1.56 ml, 10.9 mM) in THF (100 ml) was added ethyloxalyl chloride (1.1 ml, 9.8 mM). After stirring overnight the reaction mixture was diluted to 400 ml with EtOAc, washed with H2O, dried (Na2SO4), filtered and concentrated in vacuo. The residue was chromatographed on Merck Silica Gel 60 (110 g, 230-400 20 mesh) with EtOAc:Hexane (3:1) as eluent. Crystallization from EtOAc:Hexane afforded pure 43 (3.6 g, 85%) as a white crystalline solid, mp=93°-94°. MS, m/e 427 (M+).

Anal. Calcd. for C22H22ClN3O4: C, 61.75; H, 5.18; N, 25 9.82. Found: C, 61.56; H, 5.29; N, 9.78.

EXAMPLE 44

Ethyl

3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-propylamine-N-oxoacetate 161

Following the procedure of Example 43, but substituting the amine 96 of Example 32 for the amine 42 afforded 44 as a yellow oil; MS, m/e 441 (M+).

Anal. Calcd. for C23H24ClN3O4: C, 62.51; H, 5.49; N, 35 9.51. Found: C, 62.41; H, 5.66; N, 9.35.

The compounds of Table 11 were synthesized from compounds 43 or 44 by standard methods.

TABLE 11

Compound Number	n	R	Melting Point	Mass Spectrum (m/e)	C,H.N
162	3	COCON(Me)OH	111-113	442(M+)	XXX
163	2	COCON(Me)OH	110-111	428(M+)	XXX
164	3	COCONHOH	183-185*	428(M+)	XXX
165	2	COCONHOH	188~189*	414(M+)	XXX
166	3	COCO ₂ H	157-159°	413(M+)	XXX

EXAMPLE 45

N-Actyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-propyl-amine (167)

To a solution of the amine 96 (0.96 g, 2.8 mM) and Et₃N (0.59 ml, 4.2 mM) in THF (25 ml) was added acetyl chloride (0.2 ml, 2.8 mM). After stirring for 1 65 tan solid (1.22 g, 45%), mp=128°-129°. MS, m/e 451 hour the reaction mixture was diluted to 200 ml with EtOAc, washed with H2O, dried, filtered and concentrated in vacuo. Crystallization from EtOAc:Et2O af-

forded pure 45 (0.78 g, 72%) as an off-white crystalline solid, $mp = 129^{\circ}-131^{\circ}$. MS, $m/e 383 (M^{+})$.

Anal. Calcd. for C21H22ClN3O2; C, 65.70; H,5.78; N, 10.95. Found: C, 65.85; H, 6.00; N, 10.88.

Following the procedure of Example 45, but substituting trimethylacetyl chloride, methanesulfonyl chloride and diethyl chlorophosphate respectively for acetyl chloride gave the compounds of Table 12.

TABLE 12 MeO

Compound Number	R	Melting Point	Mass Spectrum (m/e)	C,H,N
168	CO-t-Bu	104-105*	425(M+)	xxx
169	SO ₂ Me	108-110°	419(M+)	XXX
170	PO(OEt) ₂	oil	477(M+)	XXX*

*i hydrate

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EXAMPLE 46

30 N-Acetyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-propanamide (171)

A white slurry of compound 29 of Example 12 (5.0 g. 13.45 mM) in CH₂Cl₂ (200 ml) and Et₃N (1.88 ml, 13.48 mM) was cooled to -10° C. under nitrogen, and treated with acetyl chloride (0.91 ml, 12.8 mM). The mixture was allowed to stir at -10° C. for 45 minutes, filtered and the filtrate concentrated in vacuo to give crude product which was purified via flash column chromatography (EtOAc) and recrystallized from Et2O to afford 46 as a white solid, mp=110°-111°. MS, m/e 413 $(\mathbf{M}+)$.

Anal. Calcd. for C₂₁H₂₀ClN₃O₄: C, 60.94; H, 4.87; N, 10.15. Found: C, 61.19; H, 5.15; N, 9.77.

EXAMPLE 47

N-Acetyl-N-acetoxy-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propanamide (172)

Following the procedure of Example 46, but employ-50 ing 2 equivalents of acetyl chloride afforded 47 as a white solid, $mp = 111^{\circ}-112^{\circ}$. MS, m/e 455 (M+).

Anal. Calcd. for C23H22ClN3O5: C, 60.59; H, 4.86; N, 9.22. Found: C, 60.52; H, 5.12; N, 9.06.

EXAMPLE 48

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(3oxobutyl)-pyrazole thiazol-2-yl hydrazone (173)

A solution of compound 23 (2.15 g, 6.06 mM) in EtOH (6.2 ml) and glacial acetic acid (0.2 ml) was warmed to 35° and 2-thiazolylhydrazine (0.698 g, 6.06 mM) was added. Stirring was continued for 80 minutes and the resulting brown solution was cooled to room temperature for 1 hour, then allowed to stand at -15° , filtered, and recrystallized from EtOH to afford 48 as a

Anal. Calcd. for C23H22ClN5S: C, 61.12; H, 4.91; N, 15.50. Found: C,60.89; H, 4.81; N, 15.12.

40

Following the procedure of Example 48, but substituting the appropriate ketone from Table 15 or aldehyde 11 for compound 23 afforded the compounds of Table 13.

TABLE 13

Compound Number	R	Melting Point	Mass Spectrum (m/e)	C.H.N
174	Н	169-170°	437(M+)	xxx
175	CH ₂ CH ₃	149-152*	465(M+)	XXX*
176	Phenyl	104-105°	513(M+)	XXX**

^{*}i hydrate

Following the procedure of Example 22, but substituting ethyl magnesium bromide, phenyl magnesium bromide and t-butyl magnesium chloride for methyl magnesium bromide gave the compounds of Table 14.

TABLE 14

Compound Number	R	Melting Point	Mass Spectrum (m/e)	C.H,N
177	Et	84-85°	370(M+)	XXX
178	Ph	107-108*	418(M+)	XXX*
179	t-Bu	127-129*	398(M+)	xxx•

*i hydrate

Following the procedure of Example 23, but substituting the appropriate alcohol from Table 14 for compound 20 afforded the compounds of Table 15.

TABLE 15

R	Melting Point	Mass Spectrum (m/e)	C.H.N
Et	89-90*	368(M+)	xxx
Ph	138-139°	416(M+)	XXX
	Et	R Point Et 89-90*	R Point (m/e) Et 89-90° 368(M+)

EXAMPLE 49

2-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3pyrazolyl]-ethyl carboxamidoxime (184)

To a suspension of nitrile 95 (1.0 g, 2.96 mM) in MeOH (6 ml) was added NaHCO₃ (0.50 g, 5.9 mM) and a solution of hydroxylamine.HCl (0.40 g, 5.9 mM) in H₂O (5 ml). The reaction was heated to reflux for 16 hours, concentrated in vacuo and the residue partitioned between H2O and CHCl3. The CHCl3 layer was dried (Na2SO4), filtered and concentrated in vacuo to a white foam. Crystallization from EtOAc afforded pure 49 (0.65 g, 59%) as a white crystalline solid, 15 mp = 132° - 134° . MS, m/e 370 (M+).

Anal. Calcd. for C19H19ClN4O2,0.25 H2O: C, 60.80; H, 5.24; N, 14.93. Found: C, 60.73; H, 5.18; N, 14.74.

EXAMPLE 50

N-Hydroxy-N-methyl-2-[5-(4-chlorophenyl)-1-(4methoxyphenyl)-3-pyrazolyl]ethylcarboximidamide Monohydrate (185)

Following the procedure of Example of 48, but sub-25 stituting N-methylhyroxylamine.HCl for hydroxylamine.HCl afforded 50 as a white solid, $mp = 106^{\circ}-110^{\circ}$. MS, m/e 384 (M+).

Anal. Calcd. for C20H21N4O2.H2O: C, 59.62; H, 5.75; N, 13.91. Found: C, 59.62; H, 5.65; N, 13.61.

Following the procedure of Example 18, but substituting octylamine for diethylamine gave the following compound.

35	Compound Number	NR ₆ R ₇	Melting Point	Mass Spectrum (m/e)	C.H.N
	186	NHC8H17	95-96*	467 (M+)	xxx

EXAMPLE 51

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methylpropanamide (187)

5-Methyl-6-(4-methylphenyl)-4,6-dioxohexanoic acid

Following the procedure employed for the synthesis of the 4,6-dioxohexanoic acids of Table 2"-AP, but substituting 4'-methylpropiophenone for the appropriately substituted acetophenone gave the title compound 5-methyl-6-(4-methylphenyl)-4,6-dioxohexanoic acid.

3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]propionic acid

Following the procedure employed for the synthesis of the pyrazole propionic acids of Table 2", but substituting compound 5-methyl-6-(4-methylphenyl)-4,6dioxohexanoic acid for the appropriate 6-aryl-4,6diketohexanoic acid gave 3-[1-(4-methoxyphenyl)-5-(4-60 methylphenyl)-4-methyl-3-pyrazolyl]propionic acid.

3-[1-(4-Methoxypehnyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methylpropanamide

Following the procedure of Example 5, but substitut-. 65 ing the propionic acid compound obtained above for the acid 12 gave 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-4-methyl-3-pyrazolyl]-N-hydroxy-N-methylpropanamide the title compound.

IN VIVO ALLEVIATION OF INFLAMMATION

Polyarthritis was induced in Lewis strain laboratory rats (weight = about 200 grams) by injection of a suspension of Mycobacterium butyricum in mineral oil into the 5 subplantar tissue of the mammal's hind paws. On day 10 after the injection, the rats were assigned to groups, and paw volumes and body weights were recorded. Paw volumes of the contralateral, uninjected hind paw were determined by mercury plethylsmography. Per oral 10 shown in Table 16, hereinafter.

(p.o.) dosing began and continued for five consecutive days thereafter. On day 14 after the initial injection, approximately four hours after the final dose was administered, paw volumes and body weights were recorded and quantitated.

Anti-inflammatory activity of the substituted pyrazole compounds is expressed as the percent inhibition of paw volume increase. The results of this study for several compounds of the structure shown below are

TABLE 16

InVivo alleviation of Inflammation in Rats !

			in Kats'	
	_	_		% INH. p.o.*
No.	R_1, R_2^2	R ₃ , R ₄ ³	X	(mpk)
1	н	4-Cl	—СH₂ОН	62% at 50
2	4-OMe	4-CI	-CH ₂ OH	$[ED_{50} = 3.6]$
3	4-OMe	4-Cl	-CON(CH ₁)OH	$[ED_{50} = 4.1]$
4	4-C1	4-Cl	-CH ₂ OH	68% at 50
7	Н	4-Cl	-CH ₂ OAc	54% at 50
8	3,4-diC1	4-C1	—CH ₂ OH	41% at 50
10	4-OMe	H	-CH ₂ OH	30% at 50
11	4-OMe	4-C1	-сно	$[ED_{50} = 2.6]$
12	4-OMc	4-C1	—CO₂H	$\{ED_{50} = 5.2\}$
13	4-OMe	4-CI	—CO ₂ Na	$[ED_{50} = 1.8]$
16	4-OMc	4-Cl	-CO ₂ (CH ₂) ₃ pyrazole	82% at 25
17	Н	4-Cl	—CO₂H	50% at 25
19	4-OMe	4-CI	—CO₂Me	69% at 40
20	4-OMe	4-C1	CH(OH)Me	19% at 40
21	4-C1	4-H	—CH ₂ OH	52% at 50
22	2-OMe	4-Ci	—CH ₂ OH	33% at 50
23	4-OMe	4-C1	-сосн,	53% at 40
24	4-OMe	4-C1	-CH ₂ OMe	64% at 25
25	4-OMe	4-Cl		18% at 25
			-CH=CH—CO₂Me	
26	4-OMe	4-Cl	-CH=NOH	700 - 24
28	4-OMe	4-Cl	-CONE ₁₂	79% at 25 44% at 25
29	4-OMe	4-Cl	-CONHOH	91% at 25
30	4-OMe	4-F	-CH ₂ OH	42% at 25
31	4-OMe	4-Cl	-CONH ₂	75% at 25
32	4-OMe	4-Cl	$-CH=CH-(CH_2)_3-$	69% at 25
			CO ₂ Na	
34	4-OMc	4-Cl		21% at 25
			-соин— он	
35	4-Br	4-Cl	-сн₂он	65% at 25
36	4-SO ₂ Me	4-Cl	-CH ₂ OH	40% at 50
37	4-CH ₃	4-C1	-CH₂OH	41% at 25
38	4-OMe	4-Cl	-CH=CH-(CH2)3-CONH2	40% at 40
3a	4-OMe	4-Cl	-CON(CH3)ONa	65% at 10
44	4-OMe	4-C1	-CON(CH ₃)OMe	69% at 25
45	4-OMe	4-F	-CON(CH3)OH	51% at 25
62	4-F	4-Cl	−CH ₂ OH	31% at 50
47	4-SMe	4-Cl	—CH ₂ OH	48% at 25
48	4-NO ₂	4-C1	−CH ₂ OH	40% at 40
51	4-OC5H11	4-C1	—сн₂он	6.4% at 30

TABLE 16-continued

$$R_1$$
 R_2
 R_3
 $N-N$
 $(CH_2)_2X$

InVivo alleviation of Inflammation in Rats¹

	_			% INH. p.o.*
No.	R_1, R_2^2	R ₃ , R ₄ ³	X	(mpk)
53	4-OMe	4-Cl	-CO2NHMe	94% at 40
54	4-OMe	4-Ph	—СН ₂ ОН	36% at 25
55	4-OMe	4-Mc	−СН2ОН	$[ED_{50} = 3.9]$
56	4-OMe	4-CF ₃	CH ₂ OH	$[ED_{50} = 3.0]$
57	4-OMe	4-Cl	CO ₂ NH(tBu)	87% at 25
58	4-OMe	4-Cl	CON(tBu)OH	47% at 25
59 60	4-OMe	4-Cl 4-Cl	CH ₂ OCOCH ₂ COCH ₃ CH ₂ OH	48% at 20 8% at 25
65	2-CF ₃ 4-OMe	4-Cl	CONHCH2CH2OH	21% at 15
66	4-OMe	4-Cl	CONHCH ₂ CO ₂ H	62% at 25
67	4-H	4-Cl	CON(CH ₃)OH	30% at 40
69	4-NH2	4-Cl	CH ₂ OH	17% at 15
72	4-OEt	4-Cl	CO ₂ H	71% at 15
74	3,4-diOMe	4-C1	CO ₂ H	17% at 40
75	4-OEt	4-Cl	CO₂Et	73% at 40
76	4-OEt	4-C1	CON(CH ₃)OH	43% at 15
79 81	4-OMe 4-OMe	4-CF ₃ 4-Cl	CON(CH):P+	$[ED_{50} = 3.2]$ 50% at 15
82	4-OMe	4-Cl	CON(OH)cyclohexyl	54% at 15
83	4-OMe	4-C1	CON(OH)Et	42% at 15
84	4-OMe	4-C1	CON(OH)Ph	27% at 40
85	4-OMe	4-Cl	CONH-dihydrothiazoyl	40% at 40
87	4-OMe	4-C1	COHNCH2CO2Et	22% at 15
88	4-OMe	4-Cl	CONHCH ₂ CONHOH	36% at 15
89	4-OMe	4-Cl	COHNCH ₂ CON(CH ₃)OH	57% at 15
90	4-OMe	4-Cl	CONHietrazole	32% at 15
91	4-OMe	4-C1	CON(OBz)COCH ₃	24% at 30 17% at 15
93 96	4-OMe 4-OMe	4-Cl 4-Cl	CH ₂ OCH ₂ CO ₂ H CH ₂ NH ₂	56% at 30
100	4-OMe	4-Cl	CONHCH(CO2E1)CH2SH	58% at 15
101	4-OMe	4-Cl	CONHCH(CO ₂ Et)CH ₂ SMe	57% at 15
102	4-OMe	4-CI	CO2NEt2	87% at 30
103	2-OMe	4-C1	CO ₂ H	55% at 10
105	4-OMe	4-Me	CO ₂ H	87% at 10
106	4-OMe	3-Me	CO ₂ H	11% at 10
117	4-OMe	3,4-di-Me	CO ₂ H	30% at 10
109	4-OMe	2-Me	CO ₂ H	1% at 10 51% at 10
110 104	4-OMe 2-OMe	4-Et 4-Cl	CO ₂ H CON(CH ₃)OH	39% at 15
111	4-OMe	4-Me	CON(CH ₃)OH	75% at 15
112	4-Cl	4-OMe	CON(CH ₃)OH	$[ED_{50} = 16.3]$
113	4-OMe	4-OMe	CON(CH ₃)OH	34% at 10
114	4-OMe	4-H	CON(CH ₃)OH	5% at 15
115	4-OMe	3-Me	CON(CH ₃)OH	35% at 10
118	4-OMe	2-Me	CON(CH ₃)OH	6% at 10
119	4-OMe	4-Et	CON(CH ₃)OH	24% at 10
. 133	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ CH ₂ CO ₂ H	$[ED_{50} = 4.7]$
130 132	4-OMe 4-OMe	4-Me 4-Cl	CON(CH3)OCOCH2CH2CO2H CON(CH3)OCOCH2CH2CH2CO2H	$[ED_{50} = 11.5]$ 30% at 10
133	4-OMe	4-C1	CON(CH ₃)OCOCH ₂ CH ₂ CO ₂ N ₈	75% at 10
134	4-OMe	4-C1	CON(CH ₃)OCOCH ₂ NMe ₂	$[ED_{50} = 12.5]$
135	4-OMe	4-C1	CON(CH ₃)OCO—c-5H ₉ NHCO ₂ —t-Bu	1% at 10
136	4-OMe	4-C1	CON(CH ₃)OCOCH ₂ CH ₂ CO—Morpholine	38% at 10
137	4-OMe	4-Cl	CON(CH3)OCOCH2CH2CONEt2	54% at 10
138	4-OMc	4-Me	CON(CH ₃)OCOCH ₂ NMe ₂	17% at 10
139	4-OMe	4-C1	CON(CH ₃)OCOCH ₂ Cl	$[ED_{50} = 6.0]$
140	4-OMe	4-Cl	CON(CH ₃)OCOCH ₃	77% at 15
141	4-OMe	4-C1	CON(CH ₃)OCOC(CH ₃) ₃	17% at 10
142	4-OMe	4-Cl	CON(CH ₃)OCOCH ₂ OMe	67% at 10
143 144	4-OMe 4-OMe	4-Cl 4-Cl	CON(OH)Pyr CON(OH)CHMeCO2Et	62% at 15 55% at 10
145	4-OMe	+CI	CON(OH)CHMeCO2Et	61% at 10
146	· 4-OMe	+CI	CON(OH)C8H17	29% at 10
				• •

TABLE 16-continued

$$R_2$$
 $N-N$
 $(CH_2)_2X$

InVivo alleviation of Inflammation in Rats 1

NI	n n-2	n. n 3	v	% INH. p.o.*
No.	R ₁ , R ₂ ²	R ₃ , R ₄ ³	X	(mpk)
151	4-OMe	4-Cl	CH ₂ NHOH	42% at 25
152	4-OMe	4-C1	CH ₂ N(OH)COCH ₃	40% at 10
153	4-OMe	4-C1	CH ₂ N(OH)CO—t-Bu	49% at 10
154	4-OMe	4-CI	CH ₂ N(OH)COC ₇ H ₁₅	11% at 10
155	4-OMe	4-Cl	CH ₂ N(OH)COPh	45% at 10
156	4-OMe	4-CI	CH ₂ N(OH)SO ₂ CH ₃	34% at 9
157	4-OMe	4-C1	CH2N(OH)COCO2Et	51% at 10
158	4-OMe	4-Cl	CH2N(OH)COCONHOH	$[ED_{50} = 33.4]$
160	4-OMe	4-Cl	NHCOCO ₂ Et	9% at 15
163	4-OMe	4-Cl	NHCOCON(Me)OH	28% at 15
164	4-OMe	4-Cl	CH2NHCOCONHOH	13% at 15
165	4-OMe	4-C1	NHCOCONHOH	41% at 15
171	4-OMe	4-CI	CON(OH)COCH ₃	62% at 10
172	4-OMe	4-Cl	CON(OAc)COCH ₃	83% at 15
173	4-OMe	4-CI	C(Me)=NNH-2-Thiazoline	39% at 15
174	4-OMc	4-C1	CH=NNA-2-Thiazoline	37% at 15
175	4-OMe	4-C1	C(Et)=NNH-2-Thiazoline	16% at 10
176	4-OMe	4-Cl	C(Ph)=NNH-2-Thiazoline	6% at 15
177	4-OMe	4-C1	CH(OH)Et	16% at 15
178	4-OMe	4-Cl	CH(OH)Ph	8% at 15
179	4-OMe	4-C1	CH(OH)—t-Bu	36% at 10
180	4-OMe	4-C1	COEt	32% at 15
181	4-OMe	4-Cl	COPh	30% at 15
185	4-OMe	4-C1	$C(\rightleftharpoons NH)N(OH)Me$	5% at 15
186	4-OMe	4-Cl	CONHC ₈ H ₁₇	37% at 10

*% INH. p.o. = Percentage inhibition of pad swelling from per oral dosages in the amount of substituted pyrazole compound shown, where "mpk" is milligrams per kilogram of rat bodyweight and "ED₅₀" is the effective dose to obtain a 50% inhibition of inflammation.

Abbreviations for substituents are as utilized in previous Tables and reaction Schemes. Additionally tBu is terriburyl and Ph is phenyl.

R₂ = hydrogen unless otherwise shown.

In addition, the results for compounds of the struc- 45 ture shown below are shown in Table 17.

the one will below the blown in 1,20th 17.	
TABLE 17	
MeO N-N	50
R_3 (CH ₂) ₂ X	55

No.	R3, R4	Y	x	% INH. p.o.* (mpk)
147	4-C1	Br	CO ₂ H	79% at 15
182	4-C1	Cl	CO ₂ H .	71% at 15
148	4-C1	Br	CONCHIOH	15% at 40
149	4-C1	Cl	CON(CH1)OH	68% at 15
150	4-Cl	Br	CONHOH	70% at 15

The present invention has been described with respect to prefered embodiments. It will be clear to those skilled in the art that modifictions and/or variations of the disclosed subject matter can be made without departing from the scope of the invention set forth herein. What is claimed is:

1. A compound having a structure that corresponds to the formula:

$$R_1$$
 $N-N$
 $(CH_2)_2X$

wherein

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 R_1 and R_3 are selected from the group consisting of halo, trifluoromethyl and methyl and X is selected from the group consisting of -C(O)-R₅ wherein R₅ is selected from the group consisting of -N(CH₃)OH, -N(t-butyl)OH, -N(i-propyl)OH, -N(cyclohexyl)OH, -N(ethyl)OH and -N(phenyl)OH or R₅ is -NHCH₂CO₂H, or X is -CH₂NH₂, -C(O)H or -C(=NOH)H.

2. A compound which is 3-[5-(4-chlorophenyl)-1-(4- 5 methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl-propanamide.

3. A compound which is 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-tert-butyl-N-hydroxy-propanamide.

4. A compound which is N-carboxymethyl-3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propanamide.

5. A compound selected from the group consisting of 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-isopropylpropanamide, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-cyclohexyl-N-hydroxypropanamide, and 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-ethyl-N-hydroxypropanamide.

6. A compound selected from the group consisting of 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-N-hydroxy-N-phenylpropanamide, 3-[5-(4-25 chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-propylamine, 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]propanal, 5-(4-chlorophenyl)-3-(3-oximino-propyl)-1-(4-methoxyphenyl)pyrazole and 3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-5-(4-tolyl)-pyrazole.

7. A compound which is 3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-N-hydroxy-N-methyl propanamide.

8. A compound having a structure that corresponds to the formula:

R₁ N N OH

wherein R₁ and R₃ are selected from the group consisting of halo, trifluoromethyl, methyl and methoxy.

opanamide.

9. A compound of claim 8 which is 5-(4-chlorophenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)pyrazole.

10. A compound of claim 8 which is 5-(4-trifluoromethylphenyl)-3-(3-hydroxypropyl)-1-(4-methoxyphenyl) pyrazole.

11. A compound of claim 8 which is 1-(4-bromophenyl)-5-(4-chlorophenyl)-3-(3-hydroxypropyl) pyrazole.

12. A pharmaceutical composition for the alleviation of inflammatory and cardiovascular disorders in mammals for topical, oral, parental and aerosol administration, comprising an effective amount of a substituted pyrazole compound of claim 1 as the active ingredient dispersed in a pharmaceutically acceptable carrier.

13. A method for alleviating inflammation in a mammal exhibiting an inflammatory response comprising administering to said mammal a pharamaceutical composition according to claim 1.

14. A method for treating inflammatory conditions of skin, including psoriasis or other dermatitis, comprising administering to said mammal a pharmaceutical composition according to claim 1.

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Exhibit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant

: Michael P. Wachter et jal.

Serial No.

: 42,661

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: April 29, 1987

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K. Briscoe

For

GROUP IZU : PHARMACOLOGICALLY ACTIVE

1.5-DIARYL-3-SUBSTITUTED-PYRAZOLES AND

METHOD FOR SYNTHESIZING THE SAME

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patouts and Trademarks, Washington, D. C.

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Dear Sir:

Your petitioner, Ortho Pharmaceutical Corporation, having its principal office in the city of Raritan, in the County of Somerset, State of New Jersey, represents that it is the Assignee of the entire right, title and interest to the subject matter disclosed in the above identified application as evidenced by an Assignment executed by the inventors of the application on April 28, 1987. The instant application bears Serial No. 42,661 and was filed on April 29, 1987 as a continuation-in-part of application Serial No. 867,996, filed May 29, 1986. A true copy of the Assignment executed by the inventors is appended hereto for ease of reference.

ORTH 518

Your petitioner, Ortho Pharmaceutical Corporation, hereby disclaims, under the provisions of 35 USC 253, the terminal part of any patent granted on application Serial No. 42.661 which would extend beyond the expiration date of any patent granted on Serial No. 867.996 and hereby agrees that any patent so granted on application Serial No. 42,661 shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to any patent granted on Serial No. 867,996, this agreement to run with any patent granted on application Serial No. 42,661 and to be binding upon the grantee, its successors or assigns.

The Terminal Disclaimer fee is submitted herewith by way of a Charge Letter Authorization (in duplicate).

Signed at New Brunswick, New Jersey, this 23 day of December, 1987.

ORTHO PHARMACEUTICAL CORPORATION

Benjamin F. Lambert Assistant Secretary

Attachment

Exhibid





Maintenance Fee Statement

4826868

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE		SML ENT	STAT
1 0000	4,826,868 00	183	930	0	07/042,661	05/02/89	04/29/87	04	ИО	PAID

ITEM ATTY DKT
NBR NUMBER

ORTH 518

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EXhibit



Schering-Plough Animal Health

Location: Schering-Plough Animal Health Schering-Plough Corporation 1095 Morris Avenue Union, New Jersey 07083-7137 Mailing Address: Schering-Plough Animal Health Schering-Plough Corporation PO Box 529 Kenilworth, New Jersey 0703:

October 25, 1996

Dr. Larry D. Rollins, Director (HFV-110)
Division of Therapeutic Drugs for Non-Food Animals
Office of New Animal Drug Evaluation
c/o Document Control Unit (HFV-199)
Center for Veterinary Medicine
Food & Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Dear Dr. Rollins:

Schering-Plough Animal Health would like to request that a file be opened for a new investigational compound, tepoxalin. This is a potent, orally active, dual cyclooxygenase and lipoxygenase inhibitor of arachidonic acid metabolism with demonstrated anti-inflammatory and analgesic activity. Tepoxalin's pharmacologic activity is tissue-selective, i.e., cycloxygenase inhibition is less pronounced in gastric tissue, thus giving tepoxalin a unique safety profile. We propose to demonstrate the effectiveness and safety of tepoxalin for inflammatory disorders in dogs.

Please find below general information on tepoxalin.

Chemical name:

5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide

CAS Number:

103475-41-8

Description:

White, crystalline material

Melting point:

125-130°C

Molecular Formula:

 $C_{20}H_{20}CIN_3O_3$

Molecular Weight:

385.85 g/mol

Descriptors:

Tepoxalin

RWJ-20485 SCH 43208 Chemical Structure:

This compound had previously been under investigational use in humans. The investigational drug brochure which had been compiled by the R. W. Johnson Research Institute, has been included for your information. Also included are several publications related to the pharmacology of tepoxalin.

We plan to contact you in the near future regarding a meeting to present our development program for tepoxalin.

If you have questions regarding this submission, please contact me at (908) 629-3391.

Sincerely,

Ruth LaCrosse-Vernimb

Regulatory Compliance Manager

La Crosse-Verrials

Enclosure

EX Mid (d



Food and Drug Administration Rockville MD 20857

INAD 9916

October 29, 1996

Ruth LaCrosse-Vernimb
Regulatory Compliance Manager
Schering-Plough Animal Health
Schering-Plough Animal Health Corporation
P.O. Box 529
Union, NJ 07083-713

RECEIVED

NOV 04 1996

REGULATORY AFFAIRS

Dear Ms. LaCrosse-Vernimb:

We acknowledge receipt of your submission dated October 25, 1996 for the establishment of an INAD for the investigational use of tepoxalin for treatment of inflammatory disorders in dogs for pursuant to the Federal Food, Drug, and Cosmetic Act, section 512(j), and 21 CFR part 511

Your submission has been assigned INAD number 9916 and has been forwarded to the proper reviewer for consideration.

Please refer to this number when submitting any future correspondence pertaining to the use of the aforementioned drug.

This letter does not authorize the use of edible products derived from treated food producing animal. If the intended use is in food producing animals, edible products of investigational animals may be used for food only with prior authorization g ranted by the U.S. Food and Drug Administration

Sincerely,

Carol Goolsby

Senior Records Technician Center for Veterinary Medicine

HFV-199

EXh M



Schering-Plough Animal Health

Schering-Plough Animal Health Corporatio 1095 Morris Avenue PO Box 3182 Union, New Jersey 07083-1982 Telephone (908) 298-4000

December 20, 2001

Dr. Melanie Berson, Director
Division of Therapeutic Drugs for Non-Food Animals (HFV-110)
c/o Document Control Unit (HFV-199)
Center for Veterinary Medicine
Food & Drug Administration
7500 Standish Place
Rockville, Maryland
20855

RE:

NADA# 141-193

ZUBRIN[™] TABLETS FOR DOGS

NEW ANIMAL DRUG APPLICATION

Dear Dr. Berson:

We refer to our NADA file 141-193 (INAD file 9916) for ZUBRIN™ Tablets for Dogs. ZUBRIN™ (Tepoxalin) Tablets are indicated for the control of pain and inflammation associated with osteoarthritis.

Data reviews for the Technical Sections for this product were conducted under INAD 9916. Within this NADA we are providing responses to CVM's questions and comments of September 19, 2001 on the TAS and TAE sections, labeling and FOI Summary. Responses to outstanding chemistry and manufacturing questions were filed on 5/3/01 completing this Technical Section.

For your convenience, we have also included data diskettes containing the following information:

Draft FOI Summary and Labeling (PI, CIS and carton)
Study 439 – Hematology and Serum chemistry SAS files

As this submission finalizes all outstanding questions, at this time, we consider this New Animal Drug Application complete and we respectfully request approval of this NADA.

ZUBRIN Tablets for Dogs NADA No. 141-193

If you have any questions regarding this submission, please contact me at (908) 629-3598 or at diane.debruin@spcorp.com.

Sincerely

Diane deBruin Regulatory Affairs Manager

"This submission contains trade secrets and confidential commercial information exempt from public disclosure under the Freedom of Information Act, and disclosure of which is prohibited under the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and FDA regulations. Pursuant to 21 C.F.R. Part 20, we hereby request advance notice and an opportunity to object if a preliminary determination is made to release information in this submission."



Food and Drug Administration Rockville MD 20857

NADA 141-193

December 31, 2001

Diane deBruin Regulatory Affairs Manager Schering-Plough Animal Health 1095 Morris Avenue / PO Box 3182 Union, NJ 07083-1982

RECEIVED

JAN 1 0 2002

REGULATORY AFFAIRS

Dear Ms. deBruin:

We acknowledge receipt of your submission dated November 20, 2001, which pertains to the establishment of a New Animal Drug Application for use of tepoxalin for the control of pain and inflammation associated with osteoarthritis in dogs.

Your submission has been assigned NADA number 141-193. Please refer to this number when submitting any future correspondence pertaining to this application.

The application is being forwarded to the appropriate division for review.

This is not an approval letter.

Technical Information Specialist Center for Veterinary Medicine

HFV-199

EX Milit

EXHIBIT XA

Formal correspondence Schering-Plough Animal Health("SPAH") and the Center for Veterinary Medicine ("CVM"), regarding Zubrin INAD #9916

DATE	ACTIVITY* DOCUMENT	SUBJECT	
10/25/1996	Letter to CVM	Submission of INAD and request for INAD #	
10/29/1996	Letter from CVM	INAD # 9916 assigned	
11/05/1996	Letter to CVM	Request for meeting to discuss dog development program	
01/20/1997	Letter to CVM	Notice of claimed investigational exemption for 1930C-61- V96-315-02	
01/20/1997	Letter to CVM	Notice of claimed investigational exemption for 1930C-61- V96-315-01	
02/03/1997	Letter from CVM	Categorical exclusion of use of the drug in dogs granted for INAD #9916	
07/24/1997	Letter to CVM	Advise CVM of the SPAHC change of address from Kenilworth, NJ to Union, NJ	
08/11/1997	Letter to CVM	Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-01	
08/11/1997	Letter to CVM	Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-02	
08/11/1997	Letter to CVM	Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-03	
08/11/1997	Letter to CVM	Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-04	
08/11/1997	Letter to CVM	Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-05	
08/15/1997	Letter from CVM	CVM acknowledgement of the SPAHC change of address	
09/02/1997	Letter from CVM	CVM acceptance of SPAHC participation in pilot program for e-mail submissions	
10/23/1997	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-10	
11/06/1997	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-08	
11/06/1997	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V97-345-09	
12/04/1997	Letter to CVM	Target Animal Safety Technical Section	
12/11/1997	Letter to CVM	Electronic Notices of claimed investigational exemption for shipment of drug for trial nos. V97-345-06 and V97-345-07	
12/23/1997	Letter to CVM	Notify CVM of one-year study	
02/11/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-01	
02/11/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-02	

DATE	ACTIVITY DOCUMENTA TYPE*	SUBJECT
02/11/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-03
02/25/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-04
02/25/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-08
02/25/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-09
03/06/1998	Letter to CVM	Revision of Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-09 submitted on 02/25/1998.
03/09/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-05
03/09/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-10
03/18/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-6
03/18/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-07
04/28/1998	Letter from CVM	Target Animal Safety Incomplete Letter; submission of electronic data file required.
07/07/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-272-03 – 2nd Shipment
07/14/1998	Letter to CVM	Submission of hard and electronic data for 26-week Target Animal Safety ("TAS") Study
08/07/1998	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. V98-372-05 - 2ND Shipment
08/10/1998	Letter to CVM	Request meeting with proposed agenda to update CVM on dog program
10/30/1998	Letter to CVM	Amendment to Final Report for Study no. 91021
12/11/1998	Letter to CVM	Request categorical exclusion be granted to provide environmental assessment for NADA
12/21/1998	Letter to CVM	Submission of one year dog safety study
12/21/1998	Letter to CVM	Submission of Target Animal Efficacy Technical Section
12/23/1998	Letter to CVM	Submission of minutes of 10/20/98 meeting with CVM
12/23/1998	Letter to CVM	Submission of CMC Technical Section
02/26/1999	Letter from CVM	Copies of the CVM minutes of the10/20/98 meeting
03/11/1999	Letter to CVM	Submission of additional information on TAS studies in response to CVM request
03/19/1999	Letter to CVM	Our proposal to submit formulation bioequivalence rationale
05/11/1999	Letter from CVM	CVM comments on CMC Section submitted 12/23/1998
07/28/1999	Letter to CVM	Response to CVM Comment Letter of 5/11/99
08/06/1999	Letter from CVM	CVM response to TAS Technical Section submitted on 7/14/98

	ACTIVITY DOCUMENT:	SUBJECT
09/20/1999	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. E99-473-01
09/21/1999	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. E99-473-02
10/21/1999	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. E99-473-03
11/04/1999	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. E99-473-04
11/04/1999	Letter to CVM	Electronic Notice of claimed investigational exemption for shipment of drug for trial no. E99-473-05
11/04/1999	Letter from CVM	CVM letter commenting on one year TAS study in dogs submitted on 12/21/1998.
12/20/1999	Letter from CVM	CVM comments on CMC, labelling, stability data, and plant CGMP inspections.
01/28/2000	Letter to CVM	TAS response to CVM questions and comments of 08/06/1999 &11/04/1999
05/04/2000	Letter from CVM	CVM comments on TAE Technical Section submitted on 12/21/1998
08/29/2000	Letter from CVM	CVM comments on TAS response of 1/28/20000
08/30/2000	Letter to CVM	Notification that DDS Scherer will manufacture the active drug substance and that the active drug substance manufacturing process is being optimized
09/22/2000	Letter to CVM	Submission of US 1000 dog field safety protocol
11/10/2000	Letter to CVM	Request teleconference with CVM regarding protocol submitted 09/22/2000
11/21/2000	Letter to CVM	Request withdrawal of US 1000 dog field safety study protocol from CVM review queue
12/14/2000	Letter to CVM	SPAH response to CVM letters of 05/04/2000 and 08/29/2000
05/03/2001	Letter to CVM	Response to CVM comment Letter of 12/20/1999 and information regarding registration of SEAC as active drug manufacturer
05/15/2001	Letter to CVM	Submission of revised adverse reactions tables for pacage insert and revised labeling
09/17/2001	Letter from CVM	CVM comments on TAE Technical Section, TAS studies, FOI, and labeling
11/02/2001	Letter from CVM	CVM Comment on the SEAC VMF

EXHIBIT XB

Formal correspondence between Schering-Plough Animal Health("SPAH") and the Center for Veterinary Medicine("CVM"), regarding Zubrin NADA# 141-193

DATE	ACTIVITY/ DOGUMENT-TYPE	SUBJECT
12/20/2001	NADA Applicant Response to CVM	Submission of NADA and response to letter of 9/17/01
12/31/2001	Letter from CVM	Acknowledgement of submission and Issuance of NADA number 141-193
02/04/2002	Letter to CVM	Annual Update of the Veterinary Master File
02/21/2002	Letter to CVM	Response to telephone conversation - support for label statements
06/06/2002	Letter to CV	Amendment - changes to blister card and proposal for the Client Information Sheet ("CIS")
08/02/2002	Letter to CVM	Amendment - submission of antipyretic data and revised Dose characterization
09/25/2002	Letter from CVM	Complete technical sections, incomplete labeling and FOI
10/01/2002	Letter to CVM	Electronic Meeting Request
10/02/2002	Letter to CVM	Agenda for meeting with CVM to discuss labeling
10/11/2002	Letter to CVM	Revised labeling/agenda for meeting
10/31/2002	Letter to CVM	Revised labeling and Freedom of Information("FOI") summary and CIS for meeting discussion
11/12/2002	Letter to CVM	Reactivation of NADA - facsimile labeling, FOI and CIS.
12/06/2002	Letter to CVM	Minutes of Nov. 6, 2002 teleconference with CVM
12/06/2002	Letter to CVM	Submission of final facsimile labeling, CIS, and FOI.
01/03/2003	Letter to CVM	Amendment - corrected labeling and FOI summary.
01/24/2003	Letter to CVM	Submission of final facsimile labeling.
03/31/2003	Letter from CVM	NADA approval.